09-24-10

08/142,474

DAE

Practitioner's Docket No. JAB0812USPCT ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,468,743 Issued: NOVEMBER 21, 1995
Expiration Date: NOVEMBER 21, 2012

Inventors: FRANS E. JANSSENS, GASTON S.M. DIELS, JOSEPH E. LEENAERTS

Title: IMIDAZO[2,1-B][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Express Mail Certificate

"Express Mail" mailing number: EV 822123754 US

Date of Deposit: September 23, 2010

I hereby certify that this **APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.710 et seq), return postcard and Exhibits 1-7:**

1. Power of Attorney Authorizing Ruby T. Hope to represent the Applicant in this matter.
2. Assignment and Recordation Notice
3. NDA approval letter
4. '743 Patent
5. Copy of the USPTO Maintenance Fee Statement
6. Certificate of Correction and Supporting Documentation
7. Description of Significant Activities of Applicant During Regulatory Review Period

are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, Mail Stop Patent Extension, P.O. Box 1450, Alexandria, VA 22313-1450.

Karen Hall Morgan
(Typed or printed name of person mailing paper or fee)

Karen Hall Morgan
(Signature of person mailing paper or fee)

09/27/2010 EEKUBAY1 00000025 100750 5468743
01 FC:1457 1120.00 DA

Express Mail Label No. EV 822123754 US
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent No.: 5,468,743 Issued: NOVEMBER 21, 1995
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Inventors: FRANS E. JANSSENS, GASTON S.M. DIELS, JOSEPH E. LEENAERTS

Title: IMIDAZO[2,1-B][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

Mail Stop Patent Extension
Commissioner for Patents
P.O. Box 1450
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APPLICATION FOR EXTENSION OF PATENT TERM (37 C.F.R. § 1.710 et seq)

Pursuant to 35 U.S.C. §156 and 37 C.F.R. § 1.710 et seq, Janssen Pharmaceutica N.V. ("Applicant") as Assignee and patent owner of the above-captioned patent, hereby petitions for an extension of the term of U.S. Patent No. 5,468,743 (the '743 Patent). In support of such Petition, Applicant provides the following information:

1. SIGNATURE REQUIREMENTS (37 C.F.R. §1.730)

A. IDENTIFICATION OF PERSON(S) SUBMITTING THE APPLICATION

I, Ruby T. Hope, represent that I am a registered patent practitioner signing on behalf of the patent owner ("Undersigned Agent"). A copy of a Power of Attorney from Applicant authorizing the Undersigned Agent to act on its behalf is attached hereto as Exhibit 1

B. RECORDAL OF ASSIGNMENT IN PTO

This application, U.S.S.N. 08/142,474, filed June 9, 1992, is a Continuation-in-Part of U.S.S.N. 07/853,631, filed March 18, 1992, which is abandoned, which is a Continuation of U.S.S.N. 07/714,486, filed June 13, 1991, which is abandoned.

An assignment of U.S.S.N. 08/142,474 was recorded: Date: November 29, 1993 at Reel/Frame: 6944/0923 from the named inventors to Janssen Pharmaceutica, N.V. The assignment and its notice of recordation are attached hereto as Exhibit 2.

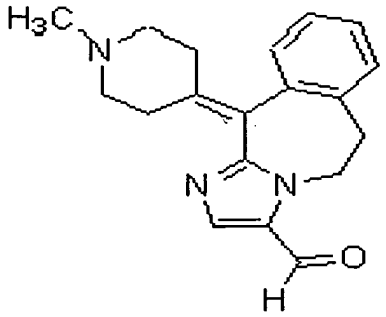
2. APPLICATION REQUIREMENTS (37 C.F.R. § 1.740)

A. IDENTIFICATION OF THE APPROVED PRODUCT (37 C.F.R. § 1.740(a)(1))

The United States Food and Drug Administration ("FDA") reviewed New Drug Application ("NDA") No. 22-134 for LASTACAFT™ (alcaftadine ophthalmic solution) ("Approved

Product"). The active ingredient of LASTACAFT™ is alcaftadine 0.25%. The chemical name for alcaftadine is 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde.

Alcaftadine has the following structural formula:



B. IDENTIFICATION OF THE FEDERAL STATUTE UNDER WHICH REGULATORY REVIEW OCCURRED (37 C.F.R. § 1.740(a)(2))

Regulatory review for the Approved Product occurred under the Federal Food Drug & Cosmetic Act, §505(b), 21 U.S.C. §.355 (New Drugs)

C. IDENTIFICATION OF THE DATE ON WHICH THE APPROVED PRODUCT RECEIVED MARKETING APPROVAL(37 C.F.R. § 1.740(a)(3))

LASTACAFT™ was approved for marketing in the United States by the FDA on July 28, 2010. A copy of the approval letter from the FDA and a subsequent communication with the FDA concerning discrepancies in the approved labeling are attached as Exhibit 3.

D. IDENTIFICATION OF THE ACTIVE INGREDIENT OF THE APPROVED PRODUCT AND PREVIOUS APPROVAL INFORMATION(37 C.F.R. § 1.740(a)(4))

LASTACAFT™ is a human drug product, the sole active ingredient of which is alcaftadine. Neither alcaftadine, not any salt or ester thereof, has been previously approved, alone or in combination, for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

E. STATEMENT CONCERNING THE TIMELY SUBMISSION OF THE APPLICATION (37 C.F.R. § 1.740(a)(5))

This application for Patent Term Extension under 35 U.S.C. §156 is being submitted within the sixty day period of 37 C.F.R. § 1.720(f). The last date this application may be submitted is September 25, 2010.

F. IDENTIFICATION OF PATENT (37 C.F.R. § 1.740(a)(6))

Name of inventors: FRANS E. JANSSENS
GASTON S.M. DIELS
JOSEPH E. LEENAERTS

Patent No.: 5,468,743

Date of issue: NOVEMBER 21, 1995

Expiration date: NOVEMBER 21, 2012

G. COPY OF THE PATENT FOR WHICH EXTENSION IS SOUGHT (37 C.F.R. § 1.740(a)(7))

A copy of the '743 Patent, including the entire specification (with claims) is attached as Exhibit 4.

H. COPIES OF RECEIPT OF MAINTENANCE FEE PAYMENT (37 C.F.R. § 1.740(a)(8))

A copy of the U.S. Patent & Trademark Office Maintenance Fee Statement and the Bibliographic Data, confirming when maintenance fees were paid for the '743 Patent is attached as Exhibit 5.

No disclaimers or reexamination certificates have issued in the '743 Patent.

A Certificate of Correction to correct the title of the published patent pursuant to 37 C.F.R. §1.322 is being filed with the Certificate of Correction Branch of the PTO concurrently with this application. Copies of the filed certificate and its supporting documentation are attached as Exhibit 6

I. IDENTIFICATION OF CLAIMS READING ON THE APPROVED PRODUCT (1.740(a)(9))

The '743 Patent claims the active ingredient of the Approved Product which is alcaftadine. The '743 Patent contains 16 claims, of which, Claims 1-5 read on alcaftadine; and Claims 6-10 read on a pharmaceutical composition containing alcaftadine, as discussed in further detail below.

Claims 1-4 claim a number of compounds including alcaftadine, which is represented by following elements of those claims.

R^1 is hydrogen

R^2 is hydrogen

R^3 is formyl

R^4 is hydrogen

R^5 is hydrogen

L is C_{1-6} alkyl in Claim 1 and C_{1-4} alkyl in Claims 2, 3, and 4.

Claim 5 claims several compounds by their chemical names, including, 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde, the chemical name of alcaftadine.

Claims 6-10 claim pharmaceutical compositions comprising a therapeutically effective amount of compounds of claims 1-5 and a pharmaceutically acceptable carrier.

J. RELEVANT DATES AND INFORMATION (37 C.F.R. §1.740(a)(10))

The '743 Patent claims a human drug.

The effective date of the investigational new drug (IND) application was July 31, 2004 and the IND No. is 66,884.

The new drug application (NDA 22-134) was initially submitted on September 28, 2009.

The NDA for LASTACAFT™ was approved for marketing by the FDA on July 28, 2010.

K. DESCRIPTION OF SIGNIFICANT ACTIVITIES OF APPLICANT DURING REGULATORY REVIEW (37 C.F.R. § 1.740(a)(11)

Attached as Exhibit 7 is a "DESCRIPTION OF SIGNIFICANT ACTIVITES OF APPLICANT DURING REGULATORY REVIEW (1.740(a)(11))" that provides a description of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the Approved Product and the significant dates applicable to such activities.

L. STATEMENT THAT PATENT IS ELIGIBLE FOR EXTENSION AND THE LENGTH OF SUCH EXTENSION (37 C.F.R. § 1.740(a)(12))

Applicant submits that the '743Patent is eligible for extension under 35 U.S.C. §156 and satisfies all of the conditions of 37 C.F.R. §1.720 as follows

i The '743 Patent claims alcaftadine, the active ingredient of a human drug product and pharmaceutical compositions containing alcaftadine. 37 C.F.R. §1.720(a)

ii The term of the '743 Patent (expiration date November 21, 2012) has never been previously extended. 37 C.F.R. §1.720(b)

iii This application is submitted in compliance with 37 C.F.R. § 1.740. 37 C.F.R. §1.720(c)

iv The Approved Product has been subject to a regulatory review period as defined in 35 U.S.C. § 156(g) before its commercial marketing or use. 37 C.F.R. §1.720(d)

v The Approved Product has received permission for commercial marketing or use and the permission for the commercial marketing or use of the Approved Product is the first received permission for commercial marketing or use under the provision of the law under which the applicable regulatory review occurred. 37 C.F.R. §1.720(e)

vi The application to extend the '743 Patent under 35 U.S.C.§ 156 is submitted within the sixty-day period beginning on the date the Approved Product first received permission for commercial marketing or use under the provisions of law under which the applicable regulatory review period occurred. 37 C.F.R. §1.720(f)

vii The term of the '743 Patent is not expired (expiration date November 21, 2012) before the submission of this application. 37 C.F.R. §1.720(g)

viii No other patent term has been extended for the same regulatory review period for the Approved Product. 37 C.F.R. §1.720(h)

Applicant submits that the length of the patent term for'743 Patent should be extended by one thousand-two-hundred and forty-six (1246) days calculated under 37 C.F.R. § 1.775, calculated as follows:

i The testing phase began on July 31, 2004 (the effective date of the NDA) and ended on September 28, 2009

ii The approval phase began on September 29, 2009 (the day of receipt of the NDA by the FDA) and ended on July 28, 2010.

iii The total number of days in the testing phase (from July 31, 2004 to September 28, 2009) is 1886 days. One half of the testing phase is 943 days.

iv The total number of days in the approval phase is (from and including September 29, 2009 to and including July 28, 2010) is 303 days from the start date to the end date, end date included

v The '743 issued on November 21, 1995 before the regulatory approval process began.

vi The marketing applicant acted with due diligence throughout the entire regulatory review period.

vii The sum of (a) the number of days in one half of the testing phase (943) and (b) the number of days in the approval phase (303) is 1246

viii The original expiration date of the patent is November 21, 2012.

ix The addition of an extension of 1246 days to the original expiration dae of the patent extends the expiration date of the patent to April 20, 2016.

x Fourteen years from the approval date of the product is July 28, 2014

xi Pursuant to 35 U.S.C. §156(c)(3), the extended term of the patent cannot exceed fourteen years from the date of product approval. The fourteen year cap does not apply since an extension of 1246 does not extend the term of the patent to July 28, 2024.

xii Pursuant to 35 U.S.C. §156(g)(6)(A), the extension period is subject to a five year limitation (for patents issued after September 24, 1984). The five year limitation does not apply since an extension of 1246 days to the term of the '743Patent is less than five years.

In view of the foregoing calculations Applicants believe that the term of the '743 Patent should be extended to April 20, 2016.

M. ACKNOWLEDGEMENT OF DUTY OF DISCLOSURE (37 C.F.R. § 1.740(a)(13))

I, Ruby T. Hope, the person signing below, acknowledge the duty to disclose to the Director of the U.S. Patent and Trademark Office and to the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension which is being sought herein. I hereby declare that all statement made herein of my own knowledge are true, and that all statement made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both under Section 1001, Title 18 of the United States Code, and that such will false statements may jeopardize the validity of this application.

N. FEE (37 C.F.R. § 1.740(a)(14))

The Application fee due is $1,120.00, 37 C.F.R.§ 1.20(j)(1).

Authorization is hereby made to charge the amount of $1,120.00, to Deposit Account No. 10-0750/JAB0812USPCT/RTH.

Please also charge any additional fees required by this paper or credit any overpayment to Deposit Account No. 10-0750/JAB0812USPCT/RTH.

O. CORRESPONDENCE & COPIES (37 C.F.R. § 1.740(a)(15))

Please direct all inquiries and correspondence relating to this application to:

Philip S. Johnson, Esq.
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933

Attn: Ruby T. Hope
Phone: (732) 524-1024
Facsimile: (732) 524-2808

Two additional copies of this application are attached, making a total of three copies being submitted.

Date: September 23, 2010

RT Hope

Ruby T. Hope
Registration No. 34,350
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933
Tel. No. 732-524-1024
Customer No. 27777

Exhibit 1

Power of Attorney Authorizing Ruby T. Hope to represent the Applicant in this matter.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE U.S. PATENT NO. 5,468,743

ISSUED: NOVEMBER 21, 1995

INVENTORS: FRANS E. JANSSENS, GASTON S.M. DIELS, JOSEPH E. LEENAERTS

FOR: IMIDAZO{2,1-B}{3}BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

Commissioner for Patents
Alexandria, VA 22313-1450

POWER OF ATTORNEY

Sir:

Janssen Pharmaceutica N.V., a company organized and existing under the laws of Belgium, having a place of business at Turnhoutseweg 30, Beerse, Belgium, B-2340, being the owner of the entire right, title and interest in and to U.S. Patent No. 5,468,743 which was granted on November 21, 1995 to FRANS E. JANSSENS, GASTON S.M. DIELS and JOSEPH E. LEENAERTS and entitled "IMIDAZO{2,1-B}{3}BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE" hereby appoints the undersigned, Ruby T. Hope, as its agent to act in its interest in this matter, and also appoints the attorneys and agents associated with Customer No. 100750, respectively and individually, each of them with full power of substitution and revocation, with regard to an application for extension of the term of U.S. Patent No. 5,468,743 and to transact all business in the U.S. Patent and Trademark Office in connection therewith.

Please direct all telephone calls to Ruby T. Hope at (732) 524-1024, and all correspondence to Philip S. Johnson at Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933.

Janssen Pharmaceutica N.V.

By: F Daelemans 31 AUGUST 2010

Name: Frank Daelemans

Title: PROXY HOLDER

Exhibit 2

Assignment and Recordation Notice

RECORDATION FORM COVER SHEET
PATENTS ONLY

To the Honorable Commissioner
of Patent and Trademarks:

Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Frans Eduard Janssens
Gaston Stanislas Marcella
Diels and Joseph Elisabeth
Leenaerts

Additional name(s) of conveying party(ies) attached?

__ Yes ✓ No

2. Name and address of receiving party(ies):

Name: Janssen Pharmaceutica N.V.

Street Address:
Turnhoutseweg 30

City: Beerse
State: Belgium Zip: B-2340

Additional name(s) & address(es) attached?

__ Yes ✓ No

3. Nature of conveyance:

✓ Assignment __ Merger
__ Security Agreement __ Change of Name
__ Other _____

Execution Date: October 13, 1993

4. Application number(s) or patent number(s):

If this document is being filed together with a new application, the execution date of the application is: October 12, 1993

A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? __ Yes ✓ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Audley A. Ciamporcero, Jr., Esq.
Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

6. Total number of applications & patents involved: 1

7. Total fee (37 CFR 3.41) $40.00

__ Enclosed
✓ Authorized to be charged to Deposit Account

8. Deposit Account Number: 10-750/JAB-812/CJM

(Attach duplicate copy of this page if paying by Deposit Account)

9. Statement and signature

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

Charles J. Metz November 29, 1993

JAB 812-PCT-US

Joint Inventors

ASSIGNMENT

Serial No.:
Filed:

WHEREAS, Frans Eduard Janssens, citizen of Belgium, residing at Tinstraat 79, B-2820-Bonheiden, Belgium, Gaston Stanislas Marcella Diels, citizen of Belgium, residing at Oosteinde 12, B-2380-Ravels, Belgium and Joseph Elisabeth Leenaerts, citizen of Belgium, residing at Potbergstraat 35, B-2310-Rijkevorsel, Belgium

(hereinafter called "Assignors"), have made certain new and useful inventions or discoveries relating to

IMIDAZO[2,1-B][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

for which they have on the 12th *day of* October, 1993, *executed an application for Letters Patent of the United States; and*

WHEREAS, JANSSEN PHARMACEUTICA N.V. a corporation of the State of Belgium, (hereinafter called "Assignee"), is desirous of acquiring Assignors' entire right, title, and interest therein:

NOW, THEREFORE, BE IT KNOWN that for and in consideration of the sum of One Dollar and other valuable considerations to them moving, the receipt of which is hereby acknowledged, Assignors have sold, assigned, and transferred, and do hereby sell, assign and transfer unto said Assignee their entire right, title and interest in and to all said inventions and discoveries disclosed in said application whose identification above by serial number and filing date, when available is hereby authorized, and in and to said application, all substitutions, divisions, and continuations thereof, and in and to all Letters Patent, United States and foreign, that may be granted for said inventions and discoveries, and in and to all extensions, renewals, and reissues thereof, the same to be held and enjoyed by said Assignee, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by Assignors if this Assignment and sale had not been made;

And Assignors hereby authorize and request the Commissioner of Patents of the United States to issue said Letters Patent in accordance with this Assignment;

And for the consideration aforesaid, Assignors covenant and agree with said Assignee that he has a full and unencumbered title to the inventions and discoveries above described and hereby assigned, which title they warrant unto said Assignee, its successors and assigns;

And for the consideration aforesaid, Assignors further covenant and agree that they will, whenever requested, but without cost to them promptly communicate to said Assignee or its representatives any facts known to them relating to said inventions and discoveries, testify in any interference or legal proceedings involving said inventions and discoveries, and execute any additional papers that may be necessary to enable said Assignee or its representatives, successors, nominees, or assigns to secure full and complete protection for the said inventions and discoveries or that may be necessary to vest in said Assignee the complete title to the said inventions and discoveries and patents hereby conveyed and to enable it to record said title.

IN TESTIMONY WHEREOF, Assignors have hereunto set their hands and seals this 13th *day of* October, 1993.

.....(L.S.)
Frans Eduard Janssens

.....(L.S.)
Gaston Stanislas Marcella Diels

.....(L.S.)
Joseph Elisabeth Leenaerts

STATE OF
COUNTY OF

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DATE: 05/10/94
TO:

N07A
AUDLEY A. CIAMPORCERO, JR., ESQ.
JOHNSON & JOHNSON, CHIEF PATENT COUNSEL
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR:
JANSSENS, FRANS E. DOC DATE: 10/13/93

ASSIGNOR:
DIELS, GASTON S. M. DOC DATE: 10/13/93

ASSIGNOR:
LEENAERTS, JOSEPH E. DOC DATE: 10/13/93

RECORDATION DATE: 11/29/93 NUMBER OF PAGES 003 REEL/FRAME 6944/0923

DIGEST : ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
JANSSEN PHARMACEUTICA N.V.
TURNHOUTSEWEG 30
BEERSE, BELGIUM B-2340

SERIAL NUMBER 8-142474 FILING DATE 11/29/93
PATENT NUMBER ISSUE DATE 00/00/00

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

08/142474

RECORDATION FORM COVER SHEET
PATENTS ONLY

Rec'd PCT/PTO 29 NOV 1993

To the Honorable Commissioner
of Patent and Trademarks:

Please record the attached original documents or copy thereof.

1. Name of conveying party(ies):

Frans Eduard Janssens
Gaston Stanislas Marcella
Diels and Joseph Elisabeth
Leenaerts

Additional name(s) of conveying party(ies) attached?

__ Yes ✓ No

2. Name and address of receiving party(ies):

Name: Janssen Pharmaceutica N.V.

Street Address:
Turnhoutseweg 30

City: Beerse
State: Belgium Zip: B-2340

Additional name(s) & address(es) attached?

__ Yes ✓ No

3. Nature of conveyance:

✓ Assignment __ Merger
__ Security Agreement __ Change of Name
__ Other _____

Execution Date: October 13, 1993

94 APR 25 AM 9:25

4. Application number(s) or patent number(s):

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A. Patent Application No.(s)

B. Patent No.(s)

Additional numbers attached? __ Yes ✓ No

5. Name and address of party to whom correspondence concerning document should be mailed:

Audley A. Ciamporcero, Jr., Esq.
Chief Patent Counsel
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

6. Total number of applications & patents involved: 1

7. Total fee (37 CFR 3.41) $40.00

__ Enclosed
✓ Authorized to be charged to Deposit Account

8. Deposit Account Number: 10-750/JAB-812/CJM

(Attach duplicate copy of this page if paying by Deposit Account)

9. Statement and signature

93436899

To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a copy of the original document.

Charles -

RECORDED FILED 930911 FRAME 923

Exhibit 3

NDA approval letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-134

NDA APPROVAL

Vistakon Pharmaceuticals, LLC
Attention: Stephen Holcroft
Vice President Worldwide Regulatory and Clinical Affairs
7500 Centurion Parkway, Suite 100
Jacksonville, FL 32256

Dear Mr. Holcroft:

Please refer to your New Drug Application (NDA) dated September 28, 2009, received September 29, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lastacaft (alcaftadine ophthalmic solution) 0.25%.

We acknowledge receipt of your amendments dated October 6, and 28, November 17, and 19, and December 10, 2009; and January 4, 28, and 29, February 25, March 4, 23, and 31, April 15, 22, and 29, May 3, 7 (2), 12, 26, and 28, June 10, and 25, and July 7, 8, 20, and 22, 2010.

This new drug application provides for the use of Lastacaft (alcaftadine ophthalmic solution) 0.25% for the prevention of itching associated with allergic conjunctivitis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Submit final printed carton and container labels that are identical to the enclosed carton and container labels, submitted on July 20 and 22, 2010, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)." Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-134.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Your application for Lastacaft (alcaftadine ophthalmic solution) 0.25% was not referred to an FDA advisory committee because there are a number of other approved ophthalmic products in this class of drugs with this indication, evaluation of the safety data did not reveal particular safety concerns that were unexpected for the class with topical ophthalmic use, and the design and results of the efficacy trials did not pose particular concerns.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. We are waiving the pediatric study requirement for ages 0 month to 24 months because studies are impossible or highly impractical because the number of pediatric patients under 24 months with allergic conjunctivitis is so small. The product is adequately labeled for pediatric patients above the age of 2 years.

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA, to CDERMedWatchSafetyAlerts@fda.hhs.gov, and to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Raphael Rodriguez, Regulatory Project Manager, at (301) 796-0798.

Sincerely,

{See appended electronic signature page}

John J. Farley, M.D., M.P.H.
Deputy Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LASTACAFT™ safely and effectively. See full prescribing information for LASTACAFT™.

LASTACAFT™ (alcaftadine ophthalmic solution)
Initial U.S. Approval: 2010

---------- INDICATIONS AND USAGE----------

LASTACAFT™ is a H_1 histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis (1)

-------DOSAGE AND ADMINISTRATION-------

Instill one drop in each eye once daily. (2)

------DOSAGE FORMS AND STRENGTHS-------

Ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL) (3)

------WARNINGS AND PRECAUTIONS----------

- To minimize the risk of contamination, do not touch dropper tip to any surface. Keep bottle tightly closed when not in use. (5.1)
- LASTACAFT™ should not be used to treat contact lens-related irritation. (5.2)
- Remove contact lenses prior to instillation of LASTACAFT™. (5.2)

----------ADVERSE REACTIONS----------

The most common ocular adverse reactions, occurring in < 4% of LASTACAFT™-treated eyes, were eye irritation, burning and/or stinging on instillation, eye redness, and eye pruritus. (6.1)

The most common non-ocular adverse reactions, occurring in < 3% of subjects with LASTACAFT™-treated eyes, were nasopharyngitis, headache and influenza (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Vistakon Pharmaceuticals, LLC at 1-800-523-6225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for Patient Counseling Information

Revised: 05/2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
LASTACAFT™ is a H_1 histamine receptor antagonist indicated for the prevention of itching associated with allergic conjunctivitis.

2 DOSAGE AND ADMINISTRATION
Instill one drop in each eye once daily.

3 DOSAGE FORMS AND STRENGTHS
Topical ophthalmic solution containing alcaftadine, 0.25% (2.5 mg/mL).

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Contamination of Tip and Solution
To minimize contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

5.2 Contact Lens Use
Patients should be advised not to wear a contact lens if their eye is red.

LASTACAFT™ should not be used to treat contact lens-related irritation.

LASTACAFT™ should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of LASTACAFT™. The preservative in LASTACAFT™, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT™.

5.3 Topical Ophthalmic Use Only

LASTACAFT™ is for topical ophthalmic use only.

6 ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Ocular Adverse Reactions
The most frequent ocular adverse reactions, occurring in < 4% of LASTACAFT™-treated eyes, were eye irritation, burning and/or stinging upon instillation, eye redness and eye pruritus.

6.2 Non-ocular Adverse Reactions
The most frequent non-ocular adverse reactions, occurring in < 3% of subjects with LASTACAFT™-treated eyes, were nasopharyngitis, headache and influenza. Some of these events were similar to the underlying disease being studied.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category B. Reproduction studies performed in rats and rabbits revealed no evidence of impaired female reproduction or harm to the fetus due to alcaftadine. Oral doses in rats and rabbits of 20 and 80 mg/kg/day, respectively, produced plasma exposure levels approximately 200 and 9000 times the plasma exposure at the recommended human ocular dose. There are however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when LASTACAFT™ is administered to a nursing woman.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

8.5 Geriatric Use
No overall differences in safety or effectiveness were observed between elderly and younger subjects.

11 DESCRIPTION

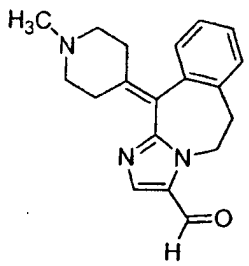
LASTACAFT™ is a sterile, topically administered H_1 receptor antagonist containing alcaftadine for ophthalmic use.

Alcaftadine is a white to yellow powder with an empirical formula of $C_{19}H_{21}N_3O$ and a molecular weight of 307.39.

Contains:
Active: alcaftadine 0.25% (2.5 mg/mL)
Preservative: benzalkonium chloride 0.005%
Inactives: edetate disodium, monobasic sodium phosphate, purified water, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH)

Chemical Name: 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5*H*-imidazo[2,1-b] [3] benzazepine-3-carboxaldehyde

Structural Formula:



The drug product has a pH of approximately 7 and an osmolality of approximately 290 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Alcaftadine is a H_1 histamine receptor antagonist and inhibitor of the release of histamine from mast cells. Decreased chemotaxis and inhibition of eosinophil activation has also been demonstrated

12.3 Pharmacokinetics
Absorption
Following bilateral topical ocular administration of alcaftadine ophthalmic solution, 0.25%, the mean plasma C_{max} of alcaftadine was approximately 60 pg/mL and the median T_{max} occurred at 15 minutes. Plasma concentrations of alcaftadine were below the lower limit of quantification (10 pg/mL) by 3 hours after dosing. The mean C_{max} of the active carboxylic acid metabolite was approximately 3 ng/mL and occurred at 1 hour after dosing. Plasma concentrations of the carboxylic acid metabolite were below the lower limit of quantification (100 pg/mL) by 12 hours after dosing. There was no indication of systemic accumulation or changes in plasma exposure of alcaftadine or the active metabolite following daily topical ocular administration.

Distribution
The protein binding of alcaftadine and the active metabolite are 39.2% and 62.7%, respectively.

Metabolism
The metabolism of alcaftadine is mediated by non-CYP450 cytosolic enzymes to the active carboxylic acid metabolite.

Excretion
The elimination half-life of the carboxylic acid metabolite is approximately 2 hours following topical ocular administration. Based on data following oral administration of alcaftadine, the carboxylic acid metabolite is primarily eliminated unchanged in the urine.

In vitro studies showed that neither alcaftadine nor the carboxylic acid metabolite substantially inhibited reactions catalyzed by major CYP450 enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Alcaftadine was not mutagenic or genotoxic in the Ames test, the mouse lymphoma assay or the mouse micronucleus assay.

Alcaftadine was found to have no effect on fertility of male and female rats at oral doses up to 20 mg/kg/day (approximately 200 times the plasma exposure at the recommended human ocular dose).

14 CLINICAL STUDIES

Clinical efficacy was evaluated in conjunctival allergen challenge (CAC) studies. LASTACAFT™ was more effective than its vehicle in preventing ocular itching in patients with allergic conjunctivitis induced by an ocular allergen challenge, both at 3 minutes post-dosing and at 16 hours post-dosing of LASTACAFT™.

The safety of LASTACAFT™ was evaluated in a randomized clinical study of 909 subjects over a period of 6 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

LASTACAFT™ (alcaftadine ophthalmic solution) 0.25% is supplied in an opaque, white low-density polyethylene bottle with a white polypropylene cap.

3 mL fill in 5 mL bottle (NDC 68669-412-03)

Storage: Store at 15-25°C (59-77°F)

17 PATIENT COUNSELING INFORMATION

17.1 Sterility of Dropper Tip

Patients should be advised to not touch dropper tip to any surface, as this may contaminate the contents.

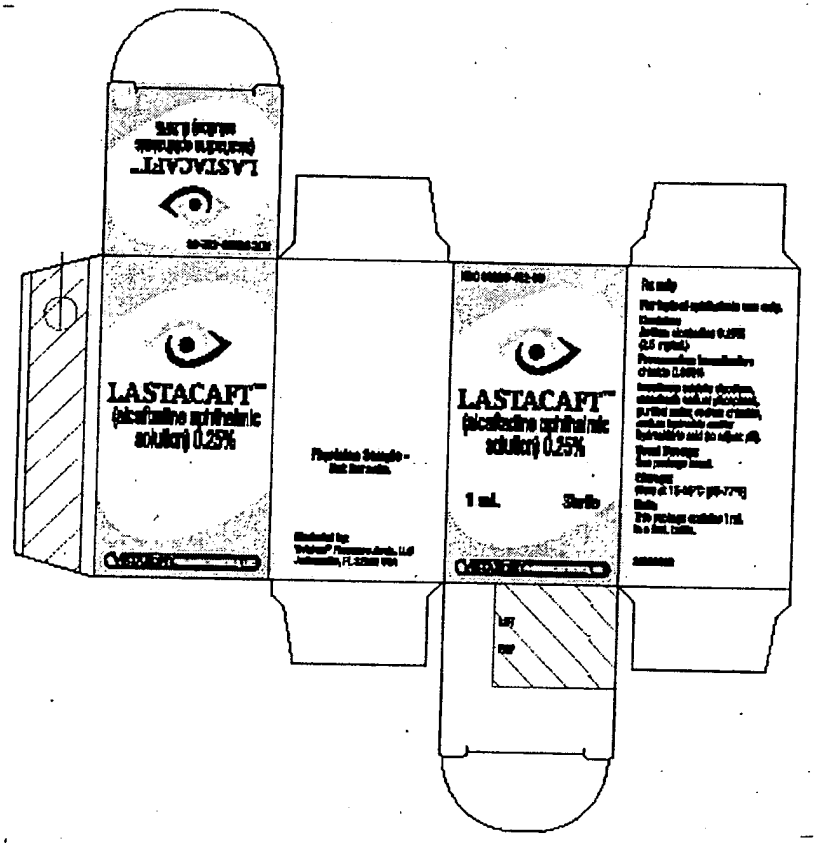
17.2 Concomitant Use of Contact Lenses

Patients should be advised not to wear a contact lens if their eye is red. Patients should be advised that LASTACAFT™ should not be used to treat contact lens-related irritation. Patients should also be advised to remove contact lenses prior to instillation of LASTACAFT™. The preservative in LASTACAFT™, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of LASTACAFT™.

Manufactured for Vistakon Pharmaceuticals, LLC
Jacksonville, FL 32256 USA

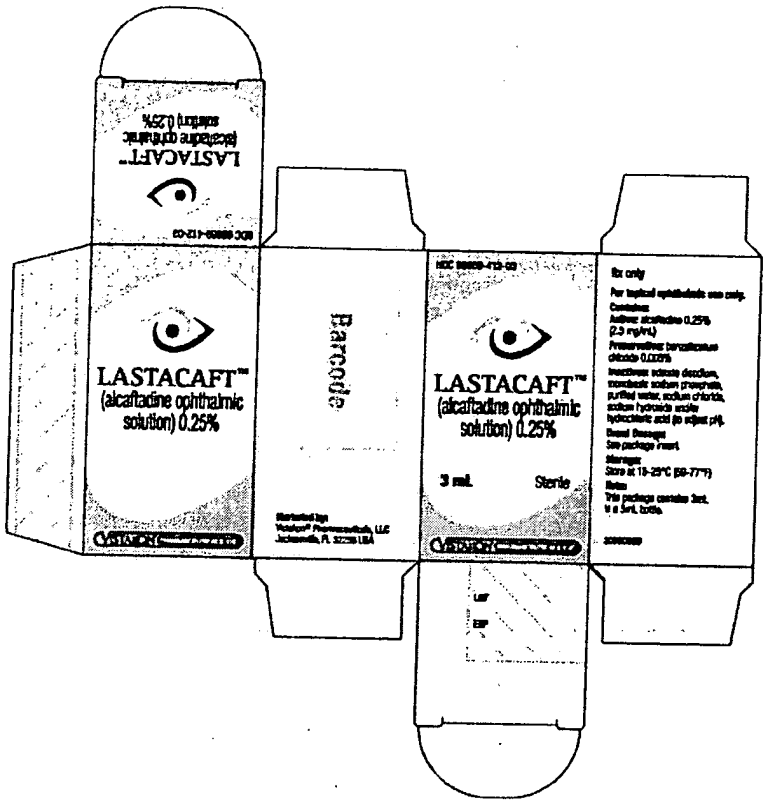
SAMPLE BOTTLE LABEL 1 ML:

SAMPLE CARTON LABEL 1 ML:



COMMERCIAL BOTTLE LABEL 3 ML:

COMMERCIAL CARTON LABEL 3 ML:



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22134	ORIG-1	VISTAKON PHARMACEUTICALS LLC	Lastacaft (alcaftadine ophthalmic solution) 0.25%

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN J FARLEY
07/28/2010

Hope, Ruby [JJCUS]

From: Bremer, Lorna-Jane [CONUS]
Sent: Tuesday, September 21, 2010 12:51 PM
To: Hope, Ruby [JJCUS]
Subject: FW: Action Letter

Ruby –
FYI re the labeling.
Lorna-Jane

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Wednesday, August 04, 2010 5:41 PM
To: Bremer, Lorna-Jane [CONUS]
Cc: Rodriguez, Raphael R
Subject: Re: Action Letter

Hi Lorna-Jean,

Thanks for alerting us to these discrepancies. These should be included in the labelings.

We will note this in the file.

Thanks.
Maureen

From: Bremer, Lorna-Jane [CONUS] <LBremer@its.jnj.com>
To: Dillon Parker, Maureen P
Cc: Rodriguez, Raphael R
Sent: Wed Aug 04 13:58:42 2010
Subject: RE: Action Letter

Dear Maureen and Raphael –
We are preparing to submit the labeling via the FDA automated drug registration and listing system (eLIST) in accordance with the attached Action Letter. In comparing this labeling to that which was submitted in Sequence 0026 and 0027, we noticed the following –

Package Insert

Section 17.3 Topical Ophthalmic Use Only (Ref. Sequence 0026) has been deleted from the PI attached to the Action Letter. Was this taken out intentionally?

Container Label – 1 mL

The statement which was added at Dr. Boyd's request – "Physician Sample – Not for sale" (Ref. Sequence 0027) does not appear on this label attached to the Action Letter.
Please let me know what you would like to do.
Thank you.
Best regards,
Lorna-Jane

Lorna-Jane Bremer, M.S., M.B.A., R.A.C.
Director Global Regulatory Affairs
Consumer & Personal Products Worldwide
Division of Johnson & Johnson Consumer Companies, Inc.
185 Tabor Road
Morris Plains, New Jersey 07950
Tel 973-385-0557

Business Cellular 862-579-8247
Fax 973-385-4300
Email LBremer@its.jnj.com

From: Dillon Parker, Maureen P [mailto:Maureen.DillonParker@fda.hhs.gov]
Sent: Wednesday, July 28, 2010 5:22 PM
To: Bremer, Lorna-Jane [CONUS]
Cc: Rodriguez, Raphael R
Subject: Action Letter

Hi Ms. Bremer,

In follow-up to my phone message, attached please find the action letter for NDA 22-134, Lastacaft.

Please let me know that you have received this e-mail and attachment.

A copy should also arrive by post shortly.

<<NDA 22-134 AP LETTER FINAL 7 28 10 to Sponsor.pdf>>

Best Regards,

Maureen
for Raphael Rodriguez, Project Manager

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Phone: 301-796-0706
Facsimile: 301-796-9881
Email: maureen.dillonparker@fda.hhs.gov

Exhibit 4

'743 Patent

US005468743A

United States Patent [19]

Janssens et al.

[11] Patent Number: 5,468,743

[45] Date of Patent: Nov. 21, 1995

[54] **IMIDAZO[2,1-B]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE**

[75] Inventors: **Frans E. Janssens**, Bonheiden; **Gaston S. M. Diels**, Ravels; **Joseph E. Leenaerts**, Rijkevorsel, all of Belgium

[73] Assignee: **Janssen Pharmaceutica N.V.**, Beerse, Belgium

[21] Appl. No.: **142,474**

[22] PCT Filed: **Jun. 9, 1992**

[86] PCT No.: **PCT/EP92/01330**

§ 371 Date: **Nov. 29, 1993**

§ 102(e) Date: **Nov. 29, 1993**

[87] PCT Pub. No.: **WO92/22551**

PCT Pub. Date: **Dec. 23, 1992**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 853,631, Mar. 18, 1992, abandoned, which is a continuation of Ser. No. 714,486, Jun. 13, 1991, abandoned.

[51] **Int. Cl.**[6] **C07D 487/04**; A61K 31/55

[52] **U.S. Cl.** **514/214**; 540/579

[58] **Field of Search** 540/579; 514/214

[56] **References Cited**

U.S. PATENT DOCUMENTS

5,008,268	4/1991	Janssens et al.	514/272
5,393,753	2/1995	Friary	514/214

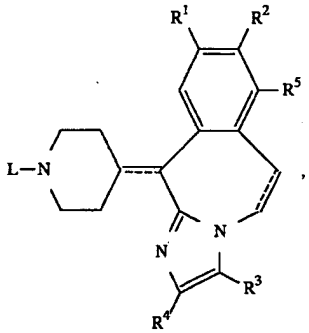
FOREIGN PATENT DOCUMENTS

0000716	2/1979	European Pat. Off. .	
WO92/6981	4/1992	WIPO	540/579

Primary Examiner—Philip I. Datlow
Attorney, Agent, or Firm—Charles J. Metz

[57] **ABSTRACT**

The present invention is concerned with novel imidazo[2,1-b][3]benzazepines of formula



(I)

the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein each of the dotted lines independently represents an optional bond; R^1 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy; R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl; R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo; R^5 represents hydrogen, C_{1-4}alkyl or halo; L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl; C_{1-4}alkyloxycarbonyl-C_{1-4}alkyloxy, hydroxycarbonylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl; or, L represents a radical of formula —Alk—Y—Het[1](a-1),—Alk—NH—CO—Het[2](a-2)or —Alk—Het[3](a-3); provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine is ecxluded, which are useful antiallergic compounds.

Compositions comprising said compounds, methods of using and processes for preparing the same.

16 Claims, No Drawings

IMIDAZO[2,1-B]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. 371 application based upon PCT Application No. PCT/EP 92/01330, filed Jun. 9, 1992, which is a continuation-in-part of U.S. applications Ser. No. 853,631, filed Mar. 18, 1992, now abandoned, which is a continuation of Ser. No. 714,486, filed Jun. 13, 1991, now abandoned.

BACKGROUND OF THE INVENTION

In WO 88/03138 there are described benzo[5,6]cycloheptapyridines which possess antiallergic and anti-inflammatory activity. In EP-A-0,339,978 there are described (benzo- or pyrido)cyclohepta heterocyclics which are useful as PAF antagonists, antihistaminics and/or anti-inflammatory agents.

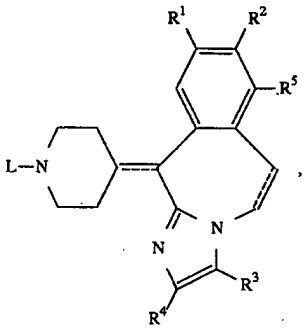
In WO 92/06981 there are described 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine and 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3] -benzazepine-11-ylidene)piperidine, the latter of which is useful as a PAF antagonist.

In the J. Med. Chem., 26 (1983), 974–980 there are described some 1-methyl-4 -piperidinylidene-9-substituted pyrrolo[2,1-b][3]benzazepine derivatives having neuroleptic properties.

The compounds of the present invention differ structurally from the cited art-known compounds by the fact that the central 7-membered ring invariably contains a nitrogen atom of a fused imidazole ring, and by their favorable antiallergic activity.

DESCRIPTION OF THE INVENTION

The present invention is concerned with novel imidazo [2,1-b][3]benzazepines of formula



(I)

the pharmaceutically acceptable addition salts and stereochemically isomeric forms thereof, wherein

each of the dotted lines independently represents an optional bond;

R^1 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy, hydroxycarbonyl-C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, aminocarbonyl or phenyl substituted with C_{1-4}alkyloxycarbonyl or hydroxycarbonyl; or,

L represents a radical of formula

—Alk—Y—Het^1 (a-1),

—Alk—NH—CO—Het^2 (a-2), or

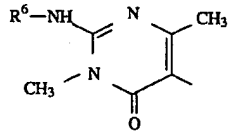
—Alk—Y—Het^3 (a-3); wherein

Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

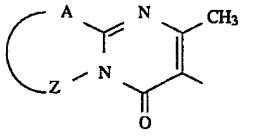
Het^1, Het^2 and Het^3 each represent furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents; pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC_{1-4}alkyl, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl or one or two C_{1-4}alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c] pyridin-2-yl; and

Het^3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula



(b-1)

or



(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

A-Z represents —S—CH=CH—, —S—CH_2—CH_2—, —S—CH_2—CH_2—CH_2—, —CH=CH—CH=CH—, —CH_2—CH_2—CH_2—CH_2—, —N(CH_3)—C(CH_3)=CH— or —CH=C(CH_3)—O—;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1 -b][3]benzazepine is ecxluded.

As used in the foregoing definitions halo defines fluoro, chloro, bromo and iodo; C_{1-4}alkyl defines straight and

branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl and 1,1-dimethylethyl; C_{1-6}alkyl defines C_{1-4}alkyl radicals as defined hereinbefore and the higher homologs thereof having from 5 to 6 carbon atoms such as, for example, pentyl and hexyl; C_{3-6}alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 3 to 6 carbon atoms such as, for example, 2-propenyl, 2-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 3-pentenyl, 3,3-dimethyl-2-propenyl, hexenyl and the like; C_{1-4}alkanediyl defines bivalent straight or branched chain hydrocarbon radicals containing from 1 to 4 carbon atoms such as, for example, methylene, 1,1-ethanediyl, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl and the like.

The term pharmaceutically acceptable addition salt as used hereinbefore defines the nontoxic, therapeutically active addition salt forms which the compounds of formula (I) may form. The compounds of formula (I) having basic properties may be converted into the corresponding therapeutically active, non-toxic acid addition salt forms by treating the free base form with a suitable amount of an appropriate acid following conventional procedures. Examples of appropriate acids are for example, inorganic acids, for example, hydrohalic acid, e.g. hydrochloric, hydrobromic and the like acids, sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.

The compounds of formula (I) having acidic properties may be converted in a similar manner into the corresponding therapeutically active, non-toxic base addition salt forms. Examples of such base addition salt forms are, for example, the sodium, potassium, calcium salts, and also the salts with pharmaceutically acceptable amines such as, for example, ammonia, alkylamines, benzathine, N-methyl-D-glucamine, hydrabamine, amino acids, e.g. arginine, lysine. The term pharmaceutically acceptable addition salts also comprises the solvates which the compounds of formula (I) may form, e.g. the hydrates, alcoholates and the like.

The term stereochemically isomeric forms as used hereinbefore defines the possible different isomeric as well as conformational forms which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically and conformationally isomeric forms, said mixtures containing all diastereomers, enantiomers and/or conformers of the basic molecular structure. All stereochemically isomeric forms of the compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some compounds of the present invention may exist in different tautomeric forms and all such tautomeric forms are intended to be included within the scope of the present invention.

Interesting compounds are those compounds of formula (I) wherein each of the dotted lines independently represents an optional bond;

R^1 represents hydrogen, halo or C_{1-4}alkyl;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen;

L represents hydrogen; C_{1-6}alkyl; C_{1-6}alkyl substituted with hydroxy, C_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl or aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, C_{1-4}alkyl or C_{1-4}alkyloxy; or,

L represents a radical of formula

—Alk—Y—Het^1 (a-1),

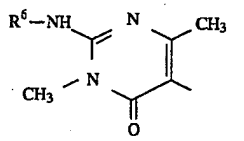
—Alk—NH—CO—Het^2 (a-2), or

—Alk—Y—Het^3 (a-3); wherein

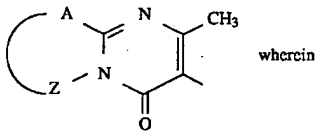
Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

Het^1, Het^2 and Het^3 each represent furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents; thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl; pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; imidazo[4,5-c]pyridin-2-yl; and Het^3 may also represent 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl, 2-oxo-3-oxazolidinyl, 2,3-dihydro-2-oxo-1H-benzimidazol-1-yl or a radical of formula


(b-1)

or


(b-2)

wherein

R^6 represents hydrogen or C_{1-4}alkyl; and

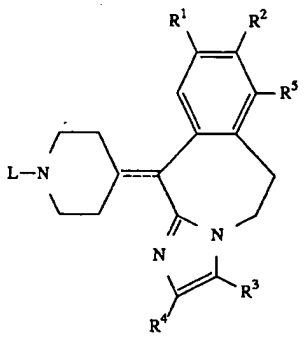
A-Z represents —S—CH=CH—, —S—CH_2—CH_2—, —S—CH_2— CH_2—CH_2—, —CH=CH—CH=CH— or CH_2—CH_2—CH_2—CH_2;

provided that 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b] [3]benzazepine is ecxluded.

Another group of interesting compounds comprises those compounds of formula (I) wherein L is C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl.

Further interesting compounds are those compounds of formula (I) wherein R^1, R^2, R^3, R^4 and R^5 represent hydrogen.

Yet another group of interesting compounds of formula (I) are those of formula



wherein R^1, R^2, R^3, R^4, R^5 and L are as defined under formula (I).

Preferred compounds are those compounds of formula (I) wherein

R^3 represents hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-4}alkyl or hydroxycarbonyl;

R^4 represents hydrogen, halo or hydroxyC_{1-4}alkyl; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylaminoC_{1-4}alkyl, aryl-C_{1-4}alkyl, propenyl, or

L is a radical of formula (a-1), (a-2) or (a-3), wherein

Het^1, Het^2, and Het^3 each represent furanyl, oxazolyl or thiazolyl each optionally substituted with C_{1-4}alkyl; thiadiazolyl optionally substituted with amino, pyridinyl; or pyrimidinyl each optionally substituted with hydroxy; imidazo[4,5-c]pyridin-2-yl; and Het^3 may also represent a radical of formula (b-2).

More preferred compounds are those preferred compounds wherein

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo or C_{1-4}alkyloxy; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, or a radical of formula (a-1), wherein Y represents NH.

Still more preferred are those more preferred compounds wherein

R^4 represents hydrogen or halo; and

L represents hydrogen, C_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl or a radical of formula (a-1), wherein Het^1 is thiazolyl, or imidazo[4,5-c]pyridin-2-yl.

The most preferred compounds are:

5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2, 1-b][3]benzazepine; 9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3]-benzazepine;

11-(1-methyl-4-piperidinylidene)-11H-imidazo[2, 1-b] [3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3]benzazepine-3methanol;

8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde;

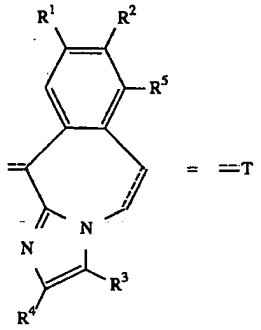
6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid;

7-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine;

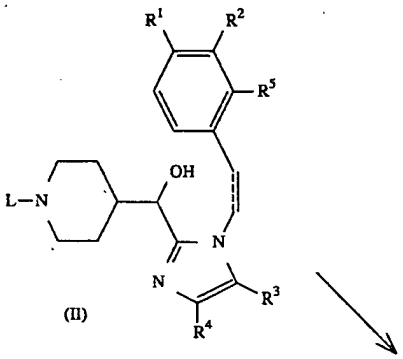
4-(8-fluoro-5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin-11 -ylidene)-1-piperidinepropanoic acid dihydrate,

the stereoisomers and the pharmaceutically acceptable acid-addition salts thereof.

In the following paragraphs there are described different ways of preparing the compounds of formula (I). In order to simplify the structural formulae of the compounds of formula (I) and the intermediates intervening in their preparation, the imidazo[2,1-b] [3]benzazepine moiety will be represented by the symbol T hereinafter.



The compounds of formula (I) can be prepared by cyclizing an alcohol of formula (II) or a ketone of formula (III).



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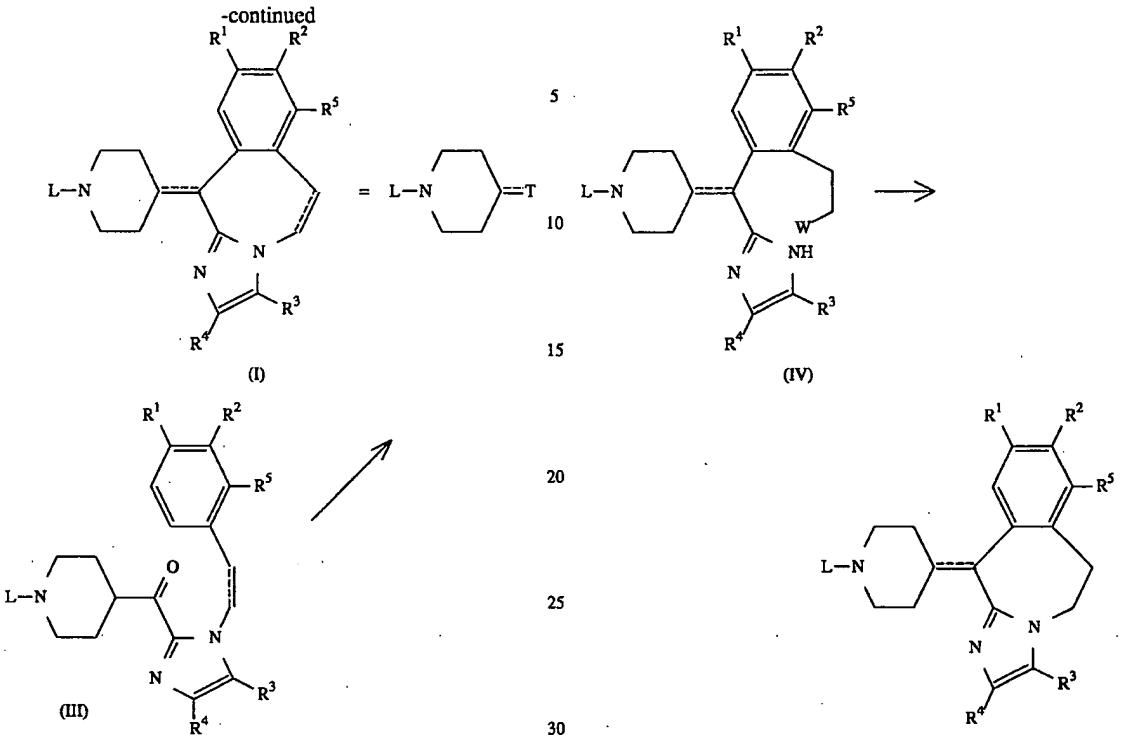


Said cyclization reaction is conveniently conducted by treating the intermediate of formula (II) or (III) with an appropriate acid, thus yielding a reactive intermediate which cyclizes to a compound of formula (I). Appropriate acids are, for example, strong acids, in particular superacid systems, e.g. methanesulfonic acid, trifluoromethanesulfonic acid, trifluoroacetic acid, methanesulfonic acid/boron trifluoride, hydrofluoric acid/boron trifluoride, or Lewis acids, e.g. aluminum chloride and the like. Obviously, only those compounds of formula (I) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. In case of superacids the reaction is preferably conducted in an excess of said acid; in case of solid Lewis acids, e.g. aluminum chloride, the reaction can be conducted by fusing the starting material and the reagent, preferably in the presence of an additional salt such as sodium chloride. The cyclodehydration reaction with trimethylsilyl iodide is conveniently conducted in a reaction-inert solvent such as, for example, a halogenated hydrocarbon, e.g. trichloromethane. Particularly noteworthy is the fact that the latter reaction also can be performed on intermediates of formula (II) or (III) wherein L represents C_{1-4}alkyloxycarbonyl; in this case—besides cyclodehydration—also cleavage of the carbamate is observed and a compound of formula (I) wherein L is hydrogen is obtained.

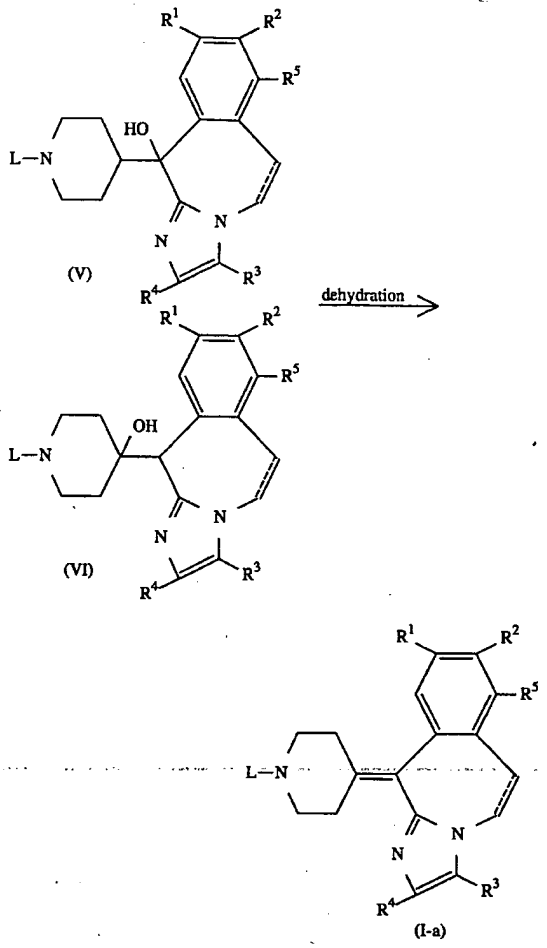
In the foregoing and following preparations, the reaction mixture is worked up following art-known methods and the reaction product is isolated and, if necessary, further purified.

The compounds of formula (I) wherein the central ring of the tricyclic moiety does not contain an optional bond may also be prepared by cyclizing an intermediate of formula (IV).

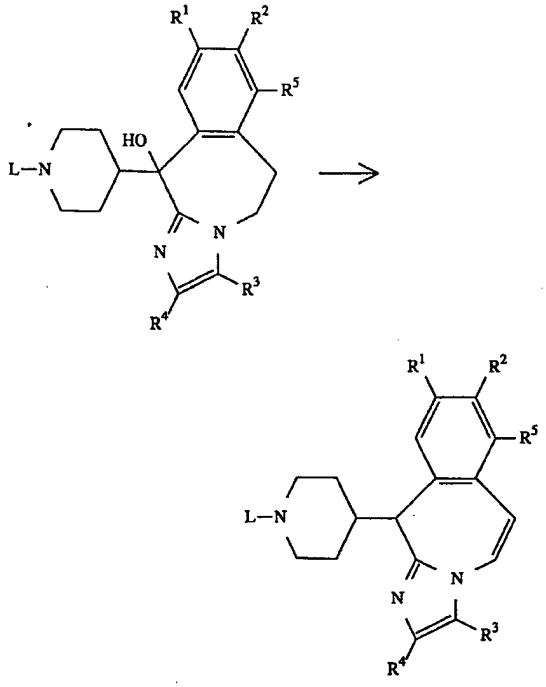
In formula (IV) and hereinafter W represents an appropriate leaving group such as, for example, halo, e.g. chloro, bromo and the like; or a sulfonyloxy group such as, for example, methansulfonyloxy, 4-methylbenzenesulfonyloxy and the like.

Said cyclization reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, NN-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction.

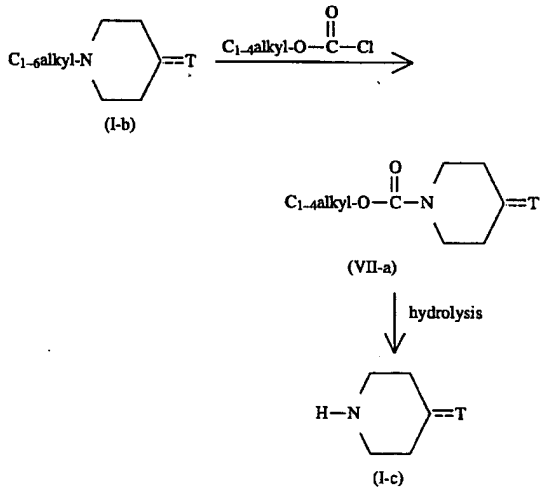
Alternatively, the compounds of formula (I) wherein a double bond exists between the piperidinyl and the imidazo [2,1-b][3]benzazepine moiety, said compounds being represented by formula (I-a), can be prepared by dehydrating an alcohol of formula (V) or (VI).



Said dehydration reaction can conveniently be conducted employing conventional dehydrating reagents following art-known methodologies. Appropriate dehydrating reagents are, for example, acids, e.g. sulfuric acid, phosphoric acid, hydrochloric acid, methanesulfonic acid, carboxylic acids, e.g. acetic acid, trifluoroacetic acid and mixtures thereof; anhydrides, e.g. acetic anhydride, phosphorus pentoxide and the like; other suitable reagents, e.g. zinc chloride, thionyl chloride, boron trifluoride etherate, phosphoryl chloride pyridine, potassium bisulfate, potassium hydroxide. In some instances said dehydration reaction may require heating the reaction mixture, more particularly up to the reflux temperature. Again, only those compounds of formula (I-a) wherein L is stable under the given reaction conditions can be prepared according to the above reaction procedure. Particularly noteworthy is the fact that the latter reaction when performed on intermediate (V) Wherein the dotted line does not represent an optional bond, in some instances may also yield a compound of formula (I) with a double bond in the tricyclic moiety and a single bond bridging the tricyclic moiety and the piperidine:



The compounds of formula (I) wherein L is C_{1-6}alkyl, said compounds being represented by the formula (I-b) can be converted into the compounds of formula (I), wherein L is hydrogen, said compounds being represented by the formula (I-c) in a number of manners. A first method involves dealkylating-carbonylating the compounds of formula (I-b) with a C_{1-4}alkylchloroformate and subsequently hydrolyzing the thus obtained compound of formula (VII-a).



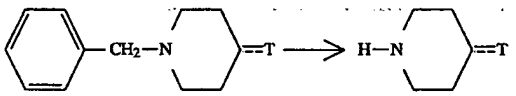
The reaction with the C_{1-4}alkylchloroformate is conveniently conducted by stirring and heating the starting material (I-b) with the reagent in an appropriate solvent and in the presence of a suitable base. Appropriate solvents are, for example, aromatic hydrocarbons, e.g. methylbenzene, dimethylbenzene, chlorobenzene; ethers, e.g. 1,2-dimethoxyethane, and the like solvents. Suitable bases are, for

example, alkali or earth alkaline metal carbonates, hydrogen carbonates, hydroxides, or organic bases such as, N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, and the like.

The compounds of formula (VII-a) are hydrolyzed in acidic or basic media following conventional methods. For example, concentrated acids such as hydrobromic, hydrochloric acid or sulfuric acid can be used, or alternatively bases such as alkali metal or earth alkaline metal hydroxides in water, an alkanol or a mixture of water-alkanol may be used. Suitable alkanols are methanol, ethanol, 2-propanol and the like. In order to enhance the rate of the reaction it is advantageous to heat the reaction mixture, in particular up to the reflux temperature.

The compounds of formula (I-b) may also be converted directly into the compounds of formula (I-c) by stirring and heating them with an α-halo-C_{1-4}alkyl chloroformate in an appropriate solvent such as, for example, a halogenated hydrocarbon, e.g. dichloromethane, trichloromethane; an aromatic hydrocarbon, e.g. methylbenzene, dimethylbenzene; an ether, e.g. 1,2-dimethoxyethane; an alcohol, e.g. methanol, ethanol, 2-propanol, optionally in the presence of a base such as, for example, an alkali or earth alkaline metal carbonate, hydrogen carbonate, hydroxide or an amine, e.g. N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, and the like.

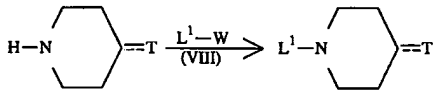
The compounds of formula (I-c) can also be prepared by debenzylating a compound of formula (I-d) by catalytic hydrogenation in the presence of hydrogen and an appropriate catalyst in a reaction-inert solvent.



(I-d) (I-c)

A suitable catalyst in the above reaction is, for example, platinum-on-charcoal, palladium-on-charcoal, and the like. An appropriate reaction-inert solvent for said debenzylation reaction is, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like, an ester, e.g. ethylacetate and the like, an acid, e.g. acetic acid and the like.

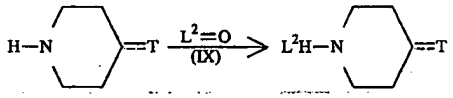
The compounds of formula (I) wherein L is other than hydrogen, said compounds being represented by formula (I-e) and said L by L^1, can be prepared by N-alkylating the compounds of formula (I-c) with a reagent of formula L^1-W (VIII).



(I-c) (I-e)

Said N-alkylation reaction can conveniently be conducted in a reaction-inert solvent such as, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; an alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., tetrahydrofuran, 1,4-dioxane, 1,1'-oxybisethane and the like; a dipolar aprotic solvent, e.g., N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, nitrobenzene, 1-methyl-2-pyrrolidinone and the like; a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane and the like; or a mixture of such solvents. The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, alkoxide, hydride, amide, hydroxide or oxide, e.g., sodium carbonate, sodium hydrogen carbonate, potassium carbonate, sodium methoxide, sodium ethoxide, potassium tert. butoxide, sodium hydride, sodium amide, sodium hydroxide, calcium carbonate, calcium hydroxide, calcium oxide and the like; or an organic base, such as, for example, an amine, e.g., N,N-diethylethanamine, N-(1-methylethyl)-2-propanamine, 4-ethylmorpholine, pyridine and the like may be utilized to pick up the acid which is liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. Somewhat elevated temperatures and stirring may enhance the rate of the reaction. Alternatively, said N-alkylation may be carried out by applying art-known conditions of phase transfer catalysis reactions.

The compounds of formula (I) wherein L is C_{1-6}alkyl or substituted C_{1-6}alkyl , said L being represented by the radical L^2H- and said compounds by formula (I-f), can also be prepared by reductive N-alkylation of the compounds of formula (I-c) with an appropriate ketone or aldehyde of formula L^2=O (IX). L^2=O represents an intermediate of formula L^2H_2 wherein two geminal hydrogen atoms have been replaced by oxygen (=O) and L^2 is a geminal bivalent C_{1-6}alkylidene radical which optionally may be substituted.

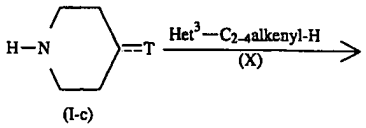


(I-c) (I-f)

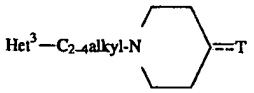
Said reductive N-alkylation reaction may conveniently be carried out by reducing a mixture of the reactants in a suitable reaction-inert solvent following art-known reductive N-alkylation procedures. In particular, the reaction mixture may be stirred and/or heated in order to enhance the reaction rate. Suitable solvents are, for example, water; C_{1-6}alkanols, e.g. methanol, ethanol, 2-propanol and the like; esters, e.g. ethyl acetate, γ-butyrolactone and the like; ethers, e.g. 1,4-dioxane, tetrahydrofuran, 1,1'-oxybisethane, 2-methoxyethanol and the like; halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like; dipolar aprotic solvents, e.g. N,N-dimethylformamide, dimethyl sulfoxide and the like; carboxylic acids, e.g. acetic acid, propanoic acid and the like; or a mixture of such solvents. The term "art-known reductive N-alkylation procedures" means that the reaction is carried out either with sodium cyanoborohydride, sodium borohydride, formic acid or a salt thereof, e.g. ammonium formate and the like reducing agents, or alternatively under hydrogen atmosphere, optionally at an increased temperature and/or pressure, in the presence of an appropriate catalyst such as, for example, palladium-on-charcoal, platinum-on-charcoal and the like. In order to prevent the undesired further hydrogenation of certain functional groups in the reactants and the reaction products, it may be advantageous to add an appropriate catalyst-poison to the reaction mixture, e.g., thiophene, quinoline-sulphur and the like. In some instances it may also be advantageous to add an alkali metal salt to the reaction mixture such as, for example, potassium fluoride, potassium acetate and the like salts.

The compounds of formula (I) wherein L represents a radical Het^3-C_{2-4}alkyl, said compounds being represented by formula (I-g) can be prepared by the addition reaction of

a compound of formula (I-c) to an appropriate alkene of formula (X).

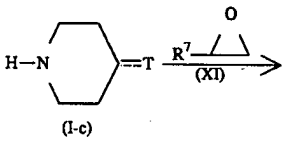


(I-c)

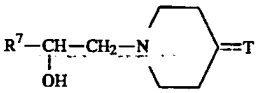


(I-g)

The compounds wherein L is 2-hydroxy-C_{2-6}alkyl, or aryloxy-2-hydroxy-C_{2-6}alkyl said compounds being represented by formula (I-h), can be prepared by reacting a compound of formula (I-c) with an epoxide (XI) wherein R^7 represents hydrogen, C_{1-4}alkyl or aryloxyC_{1-4}alkyl.



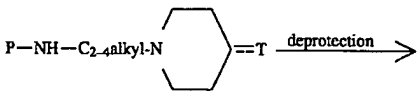
(I-c)



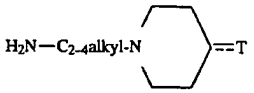
(I-h)

The reaction of (I-c) with respectively (X) or (XI) can be conducted by stirring and, if desired, heating the reactants in a reaction-inert solvent such as, for example, a ketone, e.g. 2-propanone, 4-methyl-2-pentanone; an ether, e.g. tetrahydrofuran; an alcohol, e.g. methanol, ethanol, 1-butanol; a dipolar aprotic solvent, e.g. N,N-dimethylformamide and the like.

The compounds of formula (VII-b) can be prepared from a compound of formula (I-i) wherein L represents P—NH—C_{2-4}alkyl and P is a protective group such as, for example, C_{1-4}alkyloxycarbonyl, following art-known deprotection methods.

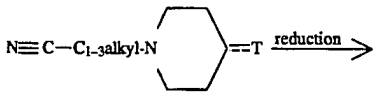


(I-i)

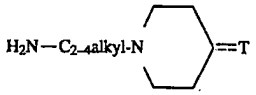


(VII-b)

The compounds of formula (VII-b) can also be prepared by reducing a compound of formula (VII-c).



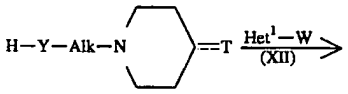
(VII-c)



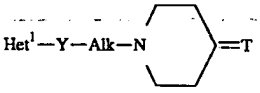
(VII-b)

Said reduction can be conducted by stirring and, if desired, heating the starting material in a hydrogen containing medium in the presence of a catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel and the like, in a suitable solvent, e.g. methanol, ethanol and the like, or by reduction with a metal hydride, e.g. lithium aluminum hydride in an ether, e.g. tetrahydrofuran.

The compounds of formula (I) wherein L is a radical of formula —Alk—Y-Het^1, said compounds being represented by formula (I-j), can be prepared by alkylating a compound of formula (I-k) with a reagent of formula (XII).

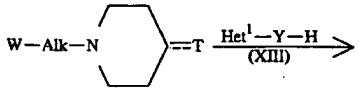


(I-k)

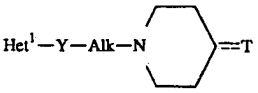


(I-j)

Alternatively, the compounds of formula (I-j) can also be prepared by reacting a compound of formula (VII-d) with a reagent of formula (XIII).



(VII-d)

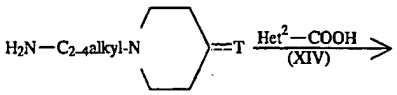


(I-j)

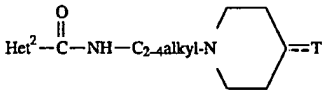
The above alkylation reactions may conveniently be conducted in a reaction-inert solvent, e.g. methylbenzene, dimethylbenzene, 2-propanone, 4-methyl-2-pentanone, 1,4-dioxane, tetrahydrofuran, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, 1-butanol and the like. The addition of an appropriate base, e.g. an alkali metal or earth alkaline metal carbonate or hydrogen carbonate, sodium hydride, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be used to pick up the acid liberated during the course of the reaction. In some instances the addition of an iodide salt, preferably an alkali metal iodide, is appropriate. In order to enhance the rate of the reaction the reaction mixture may be heated.

The compounds of formula (I) wherein L represents a

radical of formula —Alk—NH—CO—Het^2, said compounds being represented by formula (I-1) can be prepared by N-acylating a compound of formula (VII-b) with a carboxylic acid of formula (XIV) or a reactive functional derivative thereof.



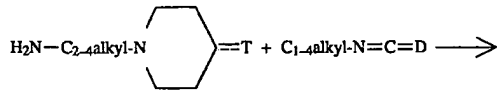
(VII-b)



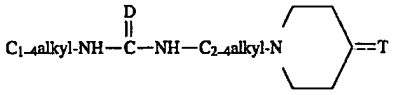
(I-l)

The reaction of (XIV) with (VII-b) may generally be conducted following art-known amidation reaction procedures. For example, the carboxylic acid may be converted into a reactive derivative, e.g. an anhydride or a carboxylic acid halide, which subsequently is reacted with (VII-b); or by reacting (XIV) and (VII-b) with a suitable reagent capable of forming amides, e.g., N,N-methanetetraylbis[cyclohexamine], 2-chloro-1-methylpyridinium iodide and the like. Said reactions are conveniently conducted in a suitable solvent such as, for example, an ether, e.g., tetrahydrofuran, a halogenated hydrocarbon, e.g., dichloromethane, trichloromethane, a dipolar aprotic solvent and the like. The addition of a base such as, for example, N,N-diethylethanamine and the like may be appropriate.

The compounds of formula (I) wherein L represents C_{1-4}alkylamino(thio)carbonylamino-C_{1-4}alkyl, said compounds being represented by the formula (I-m), can be prepared from the compounds of formula (VII-b) by reaction with a C_{1-4}alkyliso(thio)cyanate in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran.

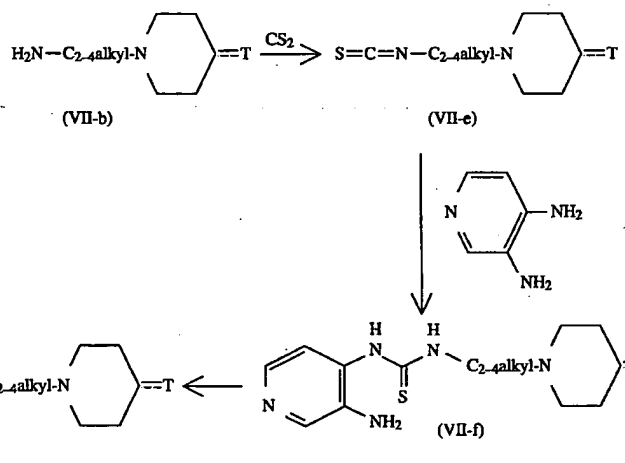


(VII-b)



D is S : (I-m-1)
D is O: (I-m-2)

The compounds of formula (I) wherein Het^1 represents an imidazo[4,5-c]pyridin-2-yl radical and Y represents NH, said compounds being represented by formula (I-n) can be prepared from a compound of formula (VII-b) according to the following reaction scheme.

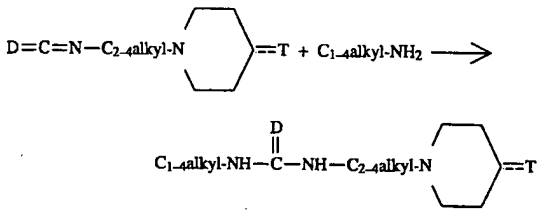


(VII-b) (VII-e)

(I-n) (VII-f)

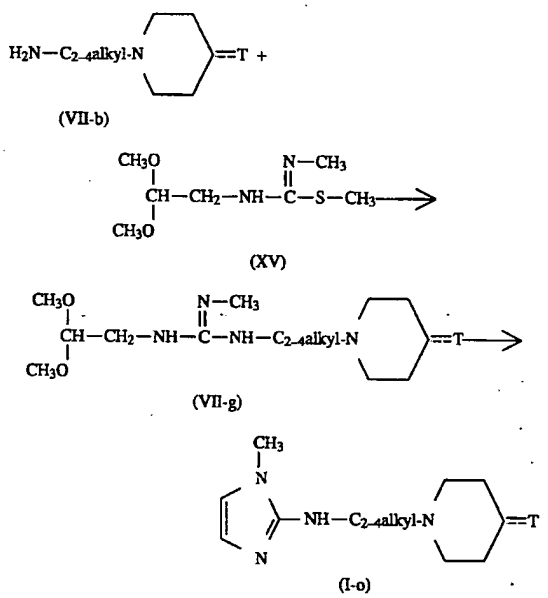
The isocyanate (VII-e) is prepared by reacting (VII-b) with carbon disulfide in the presence of a dehydrating reagent such as N,N-methanetetraylbis[cyclohexanamine] in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran. The isothiocyanate is reacted with 3,4-diaminopyridine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran, and the resulting thiourea is cyclized by treatment with an appropriate metal oxide such as mercury(II)oxide. In certain instances if may be appropriate to supplement the reaction mixture with a small amount of sulfur.

The compound (VII-e) or the corresponding isocyanate can also be employed to prepare compounds of formula (I-m), by reacting (VII-e) or the corresponding isocyanate with a C_{1-4}alkylamine in a reaction-inert solvent such as an ether, e.g. tetrahydrofuran.



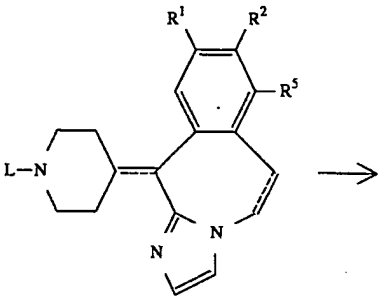
D is S : (I-m-1)
D is O: (I-m-2)

The compounds of formula (I) wherein Het^1 represents an imidazole and Y represents NH, said compounds being represented by formula (I-o) can be prepared from the compounds (VII-b) according to the following reaction scheme.

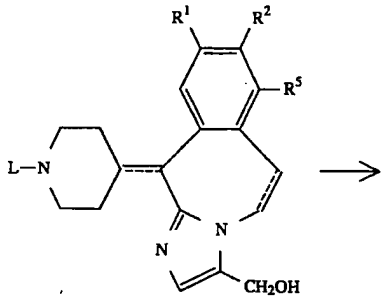


The compound (VII-b) is reacted with a reagent of formula (XV) in a reaction-inert solvent such as an alcohol, e.g. 2-propanol and the thus obtained intermediate (VII-g) is cyclized by treatment with an acidic aqueous solution, such as a hydrochloric acid aqueous solution.

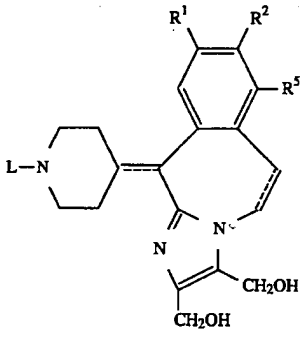
The compounds of formula (I) wherein R^3 and/or R^4 represent hydroxymethyl can be prepared by formylating the compounds of formula (I), wherein R^3 and/or R^4 are hydrogen, said compounds being represented by the formula (I-p) with formaldehyde, optionally in the presence of an appropriate carboxylic acid-carboxylate mixture such as, for example, acetic acid-sodium acetate and the like. In order to enhance the rate of the reaction, the reaction mixture is advantageously heated up to the reflux temperature.



(I-p)



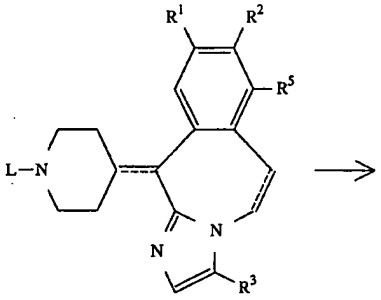
(I-q)



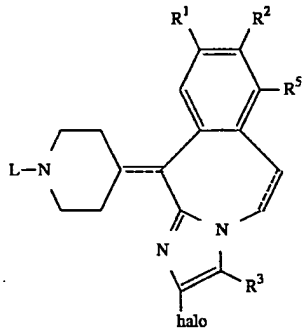
(I-r)

The thus obtained compounds (I-q) and (I-r) can be further oxidized to the corresponding aldehyde or carboxylic acid by reaction with suitable reagents such as, for example, manganese(IV)oxide, respectively, silver nitrate.

The compounds of formula (I) wherein R^4 is halo, said compounds being represented by formula (I-s), can be prepared by halogenating the compounds of formula (I), wherein R^4 is hydrogen, said compounds being represented by the formula (I-t).



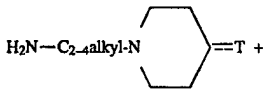
(I-t)



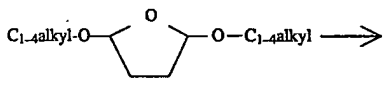
(I-s)

Said halogenation reaction can conveniently be conducted by treating the starting material with dihalide in an appropriate solvent such as, for example, a carboxylic acid, e.g. acetic acid, optionally in admixture with a carboxylate salt, e.g. sodium acetate. In order to enhance the rate of the reaction, the reaction mixture may be heated.

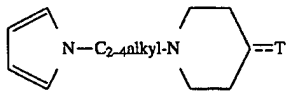
The compounds of formula (I) wherein Het^3 represents a pyrrolyl radical, said compounds being represented by the formula (I-u), can be prepared by reacting a compound of formula (VII-b) with a reagent of formula (XVI).



(VII-b)

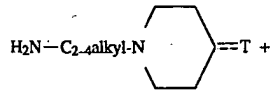


(XVI)

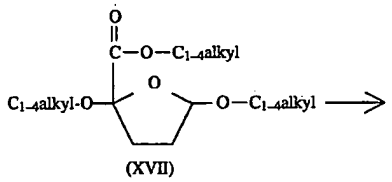


(I-u)

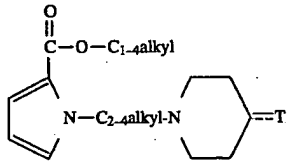
In a similar way, the compounds of formula (I) wherein Het^3 represents a 2-C_{1-4}alkyloxycarbonyl-1-pyrrolyl radical, said compounds being represented by the formula (I-v), can be prepared by reacting a compound of formula (VII-b) with a reagent of formula (XVII).



(VII-b)



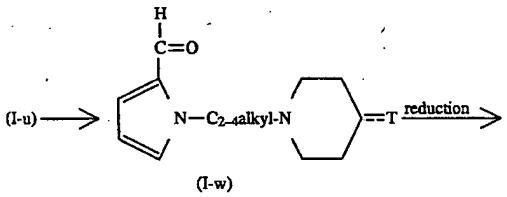
(XVII)



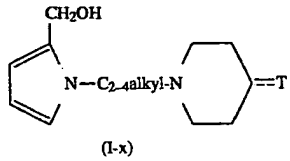
(I-v)

The above reactions of (VII-b) with (XVI) and (XVII), respectively, preferably are conducted in the presence of an acid, such as, for example, acetic acid.

Further, the compounds of formula (I-u) may be converted in the corresponding aldehyde and alcohol compounds, said compounds being represented by the formulae (I-w) and (I-x), respectively, by the following reaction sequence.



(I-w)

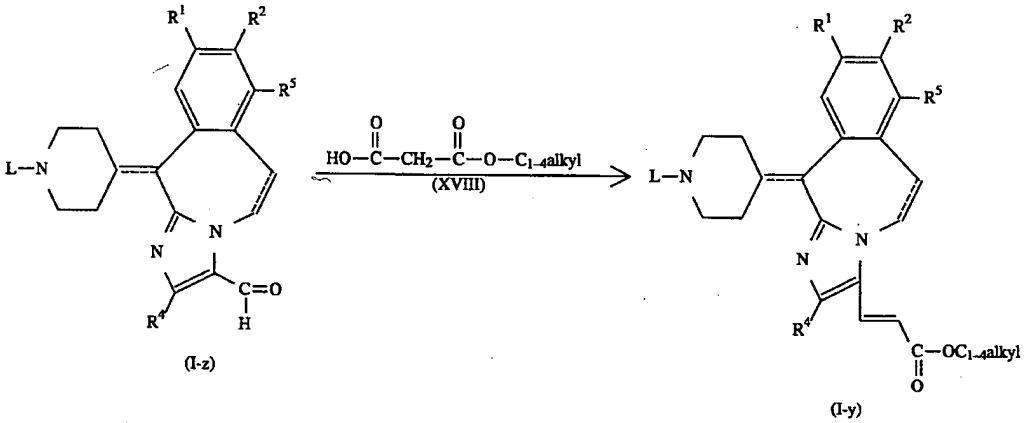


(I-x)

The formylation of (I-u) into (I-w) can conviently be conducted in a reaction-inert solvent such as, for example, a dipolar aprotic solvent, e.g. N,N-dimethylformamide, N,N-dimethylacetamide and the like, in the presence of a formylating reagent such as, for example, phosphoryl chloride, zinc cyanide and hydrochloric acid, trichloromethane and hydroxide ions, and the like. The compounds of formula (I-w) can be reduced into the compounds of formula (I-x) in a reaction-inert solvent, such as, for example, an alcohol, e.g. methanol, ethanol, 2-propanol and the like in the presence of an appropriate reductant, such as, for example, metallic hydrides, e.g. lithium aluminium hydride, sodium borohydride, sodium cyanoborohydride, and the like.

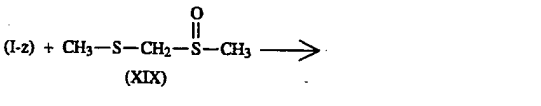
The compounds of formula (I-v) and (I-w), can be converted in the corresponding compounds of formula (I) wherein Het^3 is a 2-hydroxycarbonyl-1-pyrrolyl radical by the hydrolysis of (I-v) in the presence of an acid or a base, or oxidation of (I-w) in the presence of a suitable oxidizing reagent.

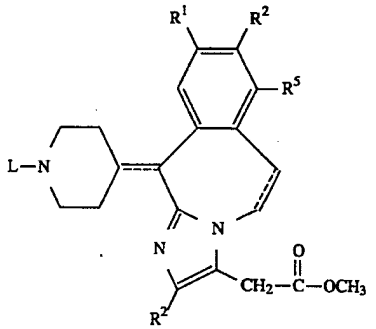
The compounds of formula (I) wherein R^3 is C_{1-4}alkyloxycarbonylethenyl, said compounds being represented by the formula (I-y), can be prepared by reacting a compound of formula (I) wherein R^3 is formyl, said compounds being represented by the formula (I-z) with a reagent of formula (XVIII) in the presence of a base e.g. piperidine, pyridine, and the like.



(I-z) (I-y)

The compounds of formula (I-y) can be further hydrolyzed into a compound of formula (I) wherein R^3 is hydroxycarbonylethenyl, in the presence of an acid or a base. The compounds of formula (I) wherein R^3 is methoxycarbonylmethyl, said compounds being represented by the formula (I-aa), can be prepared by reacting a compound of formula (I-z) with a reagent of formula (XIX) in the presence of benzyltrimethyl ammonium hydroxide in a reaction-inert solvent e.g. tetrahydrofuran.





(I-aa)

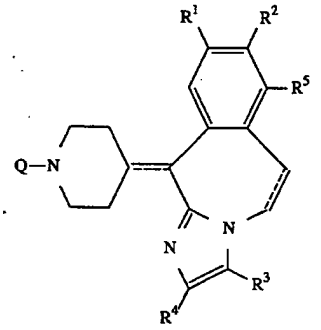
The compounds of formula (I-aa) can be further hydrolyzed into a compound of formula (I) wherein R^3 is hydroxycarbonylmethyl, in the presence of an acid or a base.

The compounds of formula (I) may further be converted into each other following art-known functional group transformation procedures.

For example, the compounds of formula (I) wherein L contains a C_{1-4}alkyloxycarbonyl moiety can be hydrolyzed into a compound of formula (I) wherein L contains a hydroxycarbonyl moiety in the presence of an acid or a base.

The compounds of formula (I) wherein L is C_{1-4}alkyloxyphenylC_{1-6}alkyl can be converted into a compound of formula (I) wherein L is hydroxyphenylC_{1-6}alkyl upon treatment with an acid, such as, for example, hydrobromic acid, hydroiodic acid or a Lewis acid, e.g. borontrifluoride, aluminiumtrichloride and the like.

The compounds of formula (VII-a to VII-g) intervening in the preparations described hereinbefore are novel and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



(VII)

the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein each of the dotted lines independently represents an optional bond,

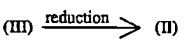
R^1, R^2, R^3, R^4 and R^5 are as defined under formula (I); and

Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with halo, cyano, amino, isothiocyanato, (4-amino-3-pyridinyl)aminothiocarbonylamino, $(CH_3O)_2CH—CH_2—NH—C(=NCH_3)—NH—$ or methylsulfonyloxy; provided that 1-acetyl-4-(5,6-dihydro-11H-imidazol[1,2-b][3]benzazepine-11-ylidene)piperidine is excluded.

Particularly interesting compounds of formula (VII) are those wherein Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, the pharmaceutically acceptable acid addition salts thereof and the stereochemically isomeric forms thereof.

In the following paragraphs there are described several methods of preparing the starting materials employed in the foregoing preparations.

The intermediates of formula (II) can be prepared from the corresponding ketones of formula (III) by reduction.

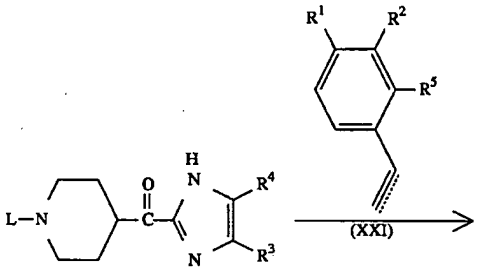


Said reduction can conveniently be conducted by reacting the starting ketone (III) with hydrogen in a solvent such as, for example, an alcohol, e.g. methanol, ethanol; an acid, e.g. acetic acid; an ester, e.g. ethyl acetate; in the presence of a hydrogenation catalyst, e.g. palladium-on-charcoal, platinum-on-charcoal, Raney Nickel.

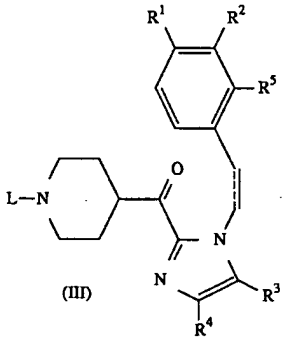
In order to enhance the rate of the reaction, the reaction mixture may be heated and, if desired, the pressure of the hydrogen gas may be raised.

Alternatively, the alcohols of formula (II) can also be prepared by reducing the ketones (III) with a reducing agent such as, for example, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride and the like in a suitable solvent such as, for example, an ether, e.g. 1,1'-oxybisethane, tetrahydrofuran and the like; an alcohol, e.g. methanol, ethanol and the like.

The ketones of formula (III) can be prepared by the addition of a compound of formula (XX) to a reagent of formula (XXI) under the reaction conditions described hereinbefore for the preparation of the compounds of formula (I-g) from the compounds of formula (I-c).

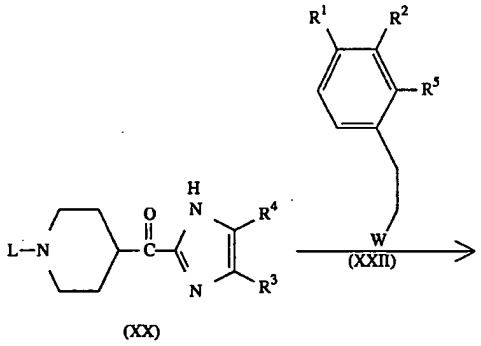


(XX)

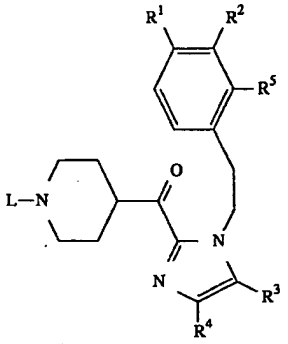


(III)

The ketones of formula (III) wherein the dotted line is not an optional bond can be prepared by N-alkylating an intermediate of formula (XX) with a reagent of formula (XXII) wherein W represents a reactive leaving group as defined hereinbefore.



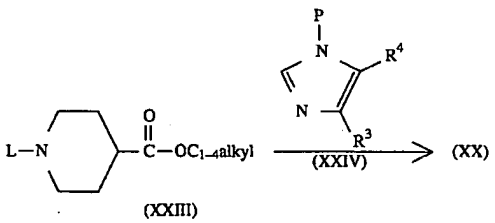
(XX)



Said N-alkylation reaction can conveniently be conducted following the procedures employed in preparing the compounds of formula (I-e) from the compounds of formula (I-c).

Further, the ketones of formula (III) wherein the dotted line is not an optional bond may also be prepared by reductive N-alkylation of the compounds of formula (XX) under the reaction conditions described for the preparation of the compounds of formula (I-f) from the compounds of formula (I-c).

The intermediates of formula (XX) are conveniently prepared from an ester of formula (XXIII) by reaction with a protected imidazole derivative of formula (XXIV) by reaction with a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a reaction-inert solvent, e.g. tetrahydrofuran, hexane, methylbenzene and the like, or a mixture thereof.



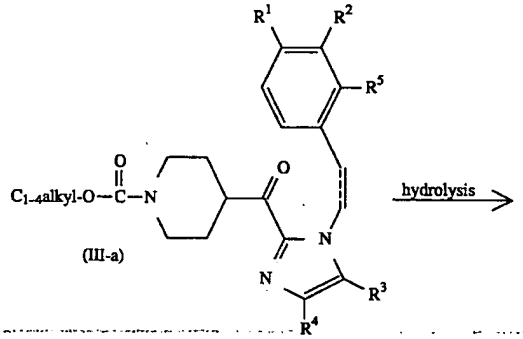
(XXIII)

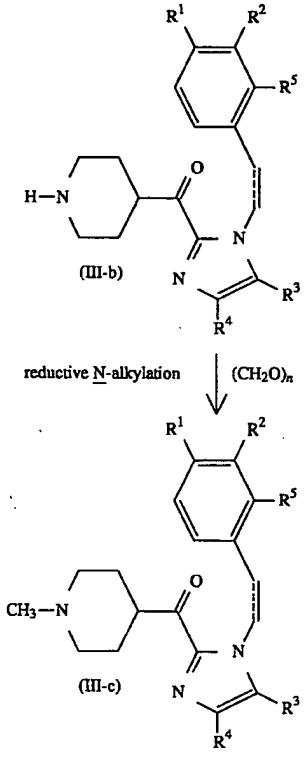
In (XXIV) P represents a protective group such as, for example, di(C_{1-4}alkoxy)methyl, C_{1-4}alkoxymethyl, benzenesulfonyl, trimethylsilylethoxymethyl, N,N-dialkylaminomethyl which can be removed by acid hydrolysis. The reaction of (XXIII) and (XXIV) is conveniently conducted at low temperatures. For example, the reagent (XXIV) may be added at a temperature between about −80° C. to about −40° C. to the strong base. Subse-

quently, the ester (XXIII) is added and the reaction mixture is allowed to warm up gently to room temperature. The thus obtained product is converted into intermediate (XX) by very mild acid hydrolysis and isolated in a conventional manner.

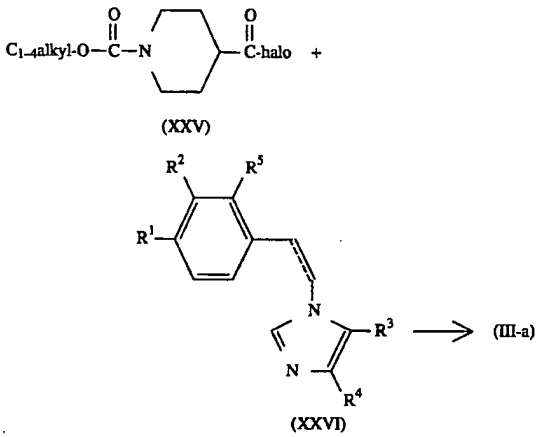
The ketones of formula (III) wherein L represents methyl, can be prepared from the ketones wherein L represents hydrogen by reductive N-alkylation with formaldehyde following the methods described hereinbefore for the preparation of the compounds of formula (I-f) from the compounds of formula (I-c).

The ketones of formula (III) wherein L represents hydrogen are prepared by hydrolysis of a carbamate of formula (III-a) in acidic or basic media following conventional methods as described hereinbefore for the preparation of compounds of formula (I-c) from the compounds of formula (I-b).





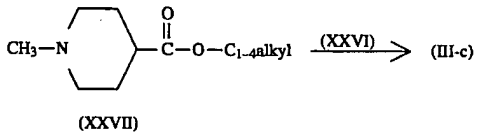
The intermediates of formula (III-a) can be prepared by reacting an acid halide of formula (XXV) with an imidazole derivative of formula (XXVI).



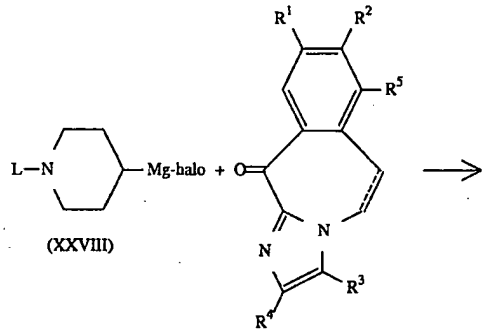
Said reaction is conveniently conducted by stirring and heating the reactants in the presence of a base such as, for example, an amine, e.g. N,N-diethylethanamine, N-methylmorpholine and the like, in a suitable solvent such as, for example, pyridine, acetonitrile or a mixture thereof.

The intermediates of formula (III-c) can also be prepared from an ester of formula (XXVII) by reaction with an imidazole of formula (XXVI) in the presence of a strong base such as, for example, methyl lithium, butyl lithium, sodium amide, a dialkyl lithium amide, e.g. diisopropyl lithium amide, or a mixture thereof, in a suitable reaction-inert solvent, e.g. tetrahydrofuran, hexane, methylbenzene and the like, or a mixture thereof.

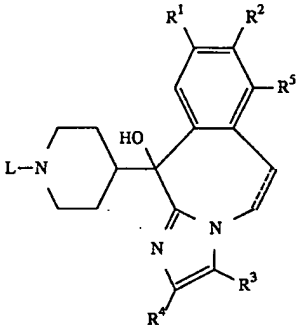
Said reaction is conveniently conducted at low temperatures. For example the reagent (XVI) may be added at a temperature between about −80° C. to about −40° C. to the strong base. Subsequently the ester is added and the reaction mixture is allowed to warm up gently to room temperature.



The intermediates of formula (V) can be prepared by addition of a Grignard reagent (XXVIII) to a ketone of formula (XXIX) in a reaction-inert solvent, e.g. tetrahydrofuran.

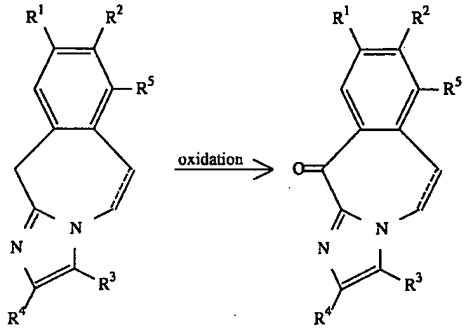


(XXVIII) (XXIX)



(V)

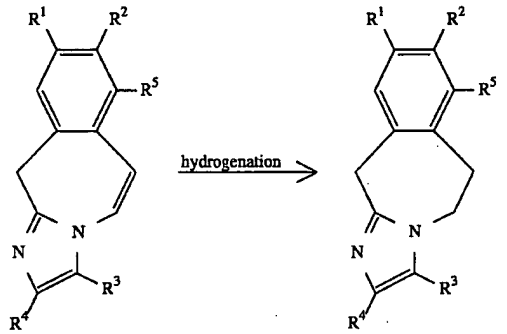
The tricyclic ketones of formula (XXIX) in turn are prepared from intermediates of formula (XXX) by oxidation with suitable oxidizing reagent in a reaction-inert solvent.



(XXX) (XXIX)

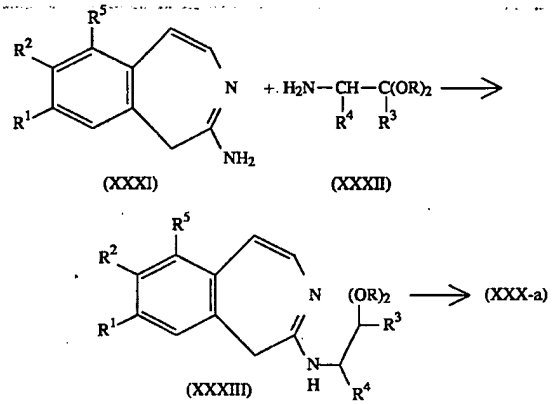
Suitable oxidizing reagents are, for example, manganese dioxide, selenium dioxide, ceric ammonium nitrate and the like. Reaction-inert solvents are, for example, halogenated hydrocarbons, e.g. dichloromethane, trichloromethane and the like.

The compounds of formula (XXX) wherein the dotted lines do not represent an optional bond, can be prepared from the corresponding compounds of formula (XXX) wherein said dotted lines do represent an optional bond, following art-known hydrogenation procedures, e.g. by reaction with hydrogen in the presence of a hydrogenation catalyst.



(XXX-a) (XXX-b)

The intermediates of formula (XXX-a) can be prepared from a benzazepine of formula (XXXI) by reaction with a reagent of formula (XXXII) and cyclization of the thus obtained intermediate (XXXIII) in an acidic medium. In (XXXII) R represents C_{1-4}alkyl or both radicals R taken together represent C_{2-6}alkanediyl, e.g. 1,2-ethanediyl, 1,3-propanediyl, 2,2-dimethyl-1,3-propanediyl.



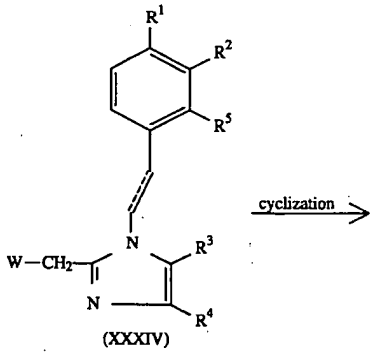
(XXXI) (XXXII)

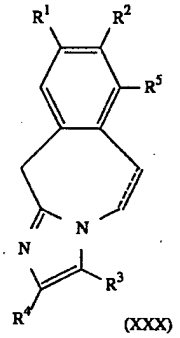
(XXXIII) (XXX-a)

The preparation of (XXXIII) is conveniently conducted by stirring and heating the reactants in a reaction-inert solvent such as, for example, an alcohol, e.g. methanol, ethanol and the like.

The cyclization reaction to the intermediates of formula (XXX-a) is conducted by stirring and heating the starting material (XXXIII) in a carboxylic acid such as, for example, acetic acid, propanoic acid, optionally in admixture with a mineral acid such as, for example, hydrochloric acid.

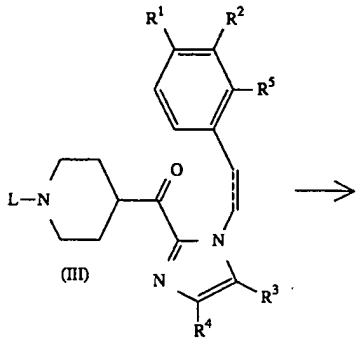
The intermediates of formula (XXX) can also be prepared from cyclization of an intermediate of formula (XXXIV).



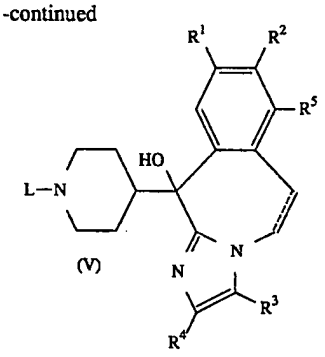

(XXX)

Said cyclization reaction is conveniently conducted in the presence of a Lewis acid, e.g. aluminium chloride, and the like. In some instances it may be appropriate to supplement the reaction mixture with a suitable amount of sodium chloride.

The intermediates of formula (V) can also be prepared from the cyclization of an intermediate of formula (III) in the presence of an acid in a reaction inert solvent.

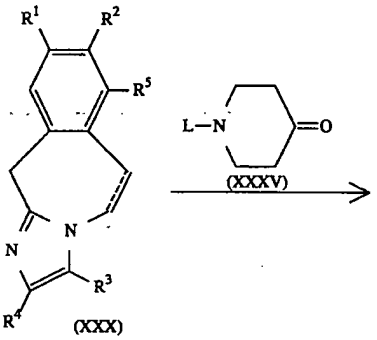

(III)

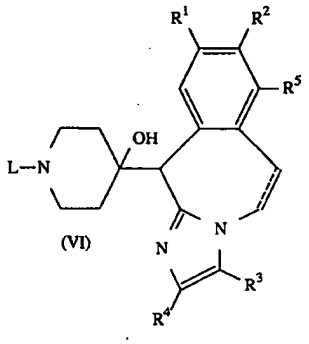
-continued


(V)

An appropriate acid in the above reaction is, for example, a Lewis acid, e.g. tin(IV)chloride and the like. A suitable reaction-inert solvent is, for example, a halogenated hydrocarbon, e.g. dichloromethane, 1,2-dichloroethane, and the like.

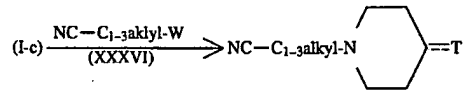
The intermediates of formula (VI) can be prepared by reaction of a ketone of formula (XXXV) with an intermediate of formula (XXX) in the precence of e.g. lithium diisopropylamide in a reaction-inert solvent, e.g. tetrahydrofuran.




(VI)

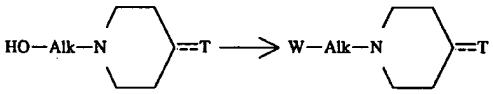
The intermediates of formula (VII-c) can be prepared by N-alkylating a compound of formula (I-c) with a reagent of

formula (XXXVI) following the procedures described hereinbefore for the preparation of the compounds of formula (I-e).



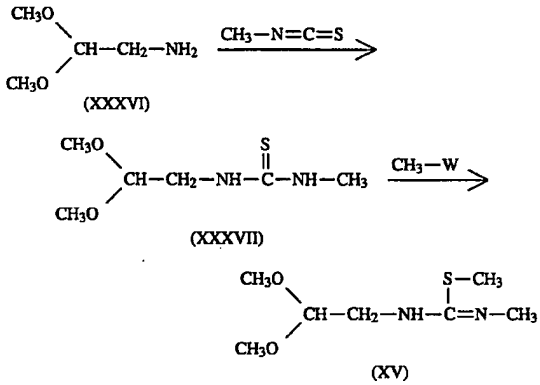
(VII-c)

The intermediates of formula (VII-d) can be prepared from the compounds of formula (I-k) wherein Y is oxygen by reaction with a halogenating reagent such as, for example, thionyl chloride, phosphorous trichloride, phosphoryl chloride and the like, or by reaction with a sulfonating reagent such as, for example, methanesulfonyl chloride, 4-methylbenzenesulfonyl chloride and the like.



(I-k) (VII-d)

The intermediates of formula (XV) can be prepared by the following reaction sequence.



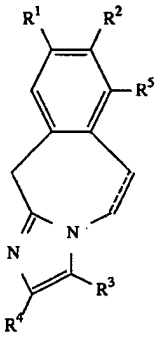
(XXXVI)

(XXXVII)

(XV)

The reaction of (XXXVI) with the isothiocyanate reagent can conveniently be conducted in a reaction-inert solvent such as, for example, an ether, e.g. tetrahydrofuran and the like. The resulting intermediate of formula (XXXVII) is methylated in a reaction-inert solvent such as, for example, a ketone, e.g. 2-propanone and the like.

The compounds of formula (XXX) intervening in the preparations described hereinbefore are novel, except for 2-methylimidazo[2,1-b][3]benzazepine, 2-phenylimidazo[2,1-b][3]benzazepine and 8,9-dimethoxyimidazo[2,1-b][3]benzazepine and have especially been developed for use as intermediates in said preparations. Consequently, the present invention also relates to novel compounds of formula



(XXX)

the addition salt forms thereof and the stereochemically isomeric forms thereof, wherein R^1, R^2, R^3, R^4, and R^5 are as defined under formula (I), 2-methylimidazo[2,1-b][3] benzazepine, 2-phenylimidazo[2,1-b][3]benzazepine and 8,9-dimethoxyimidazo[2,1-b][3]benzazepine being excluded.

The compounds of formula (I) and some of the compounds of formula (VII), in particular those wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, the pharmaceutically acceptable acid addition salts and stereochemically isomeric forms thereof possess useful pharmacological properties. In particular they are active antiallergic agents, which activity can clearly be demonstrated by he test results obtained in a number of indicative tests.

Antihistaminic activity can be demonstrated in

'Protection of Rats from Compound 48/80—induced Lethality' test (Arch. Int. Pharmacodyn. Ther., 234, 164–176, 1978);

'Histamine—induced Lethality in Guinea Pigs' test (Arch. Int. Pharmacodyn. Ther., 251, 39–51,1981);

and the broad antiallergic activity can be demonstrated in

'Passive cutaneous anaphylaxis in Rats' test (Drug Dev. Res., 5, 137–145, 1985) (For some compounds this test has been modified by replacing compound 48/80 by Ascaris allergens) and the

'Ascaris Allergy in Dogs' test (Arch. Int. Pharmacodyn. Ther., 251, 39–51, 1981 and Drug Dev. Res., 8, 95–102, 1986).

The compounds of the present invention show a broad spectrum antiallergic profile as is evidenced by the results obtained in the diversity of test procedures cited hereinbefore.

A second advantageous feature of the compounds of the present invention resides in their excellent oral activity; the present compounds when administered orally have been found to be practically equipotent with the same being administered subcutaneously.

A particularly important asset of most of the present compounds is their lack of sedating properties at therapeutic dose levels, a troublesome side effect associated with many antihistaminic and antiallergic compounds. The non-sedating properties of the present compounds can be demonstrated, for example, by the results obtained in studying the sleep-wakefulness cycle of the rat (Psychopharmacology, 97, 436–442, (1989)).

Another interesting feature of the present compounds relates to their fast onset of action and the favorable duration of their action.

In view of their antiallergic properties, the compounds of

formula (I) and (VII), wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, and their acid addition salts are very useful in the treatment of broad range of allergic diseases such as, for example, allergic rhinitis, allergic conjunctivitis, chronic urticaria, allergic asthma and the like.

In view of their useful antiallergic properties the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the antiallergic compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carder, which carder may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on or as an ointment. Acid addition salts of the subject compounds due to their increased water solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carder. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

The present invention also relates to a method of treating warm-blooded animals suffering from said allergic diseases by administering to said warm-blooded animals an effective antiallergic amount of a compound of formula (I) and (VII), wherein Q is (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino or a pharmaceutically acceptable acid addition salt form thereof.

In general it is contemplated that an effective antiallergic amount would be from about 0.001 mg/kg to about 20 mg/kg body weight, and more preferably from about 0.01 mg/kg to about 5 mg/kg body weight.

The following examples are intended to illustrate and not to limit the scope of the present invention in all its aspects.

EXPERIMENTAL PART

A. Preparation of the intermediates

Example 1

a) To a cooled mixture of 54.2 g of 1-(2-phenylethyl)-1H-imidazole, 34.7 g of N,N-diethylethanamine and 50 ml of pyridine there were added dropwise 69.2 g of ethyl 4-chlorocarbonyl-1-piperidinecarboxylate-(temp.≦0.20° C.) and then 30 ml of acetonitrile. The whole was stirred for 2 hours at room temperature and for 4 hours at reflux temperature. After cooling, there were added 30 ml NaOH 50% and refluxing was continued for ½ hour. The cooled reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 97:3). The eluent of the desired fraction was evaporated and the residue was dried, yielding 38 g (33.9%) of ethyl 4-[[1-(2-phenylethyl)-1H -imidazol-2-yl]carbonyl]-1-piperidinecarboxylate (interm. 1).

In a similar manner there was also prepared:
ethyl 4-[[1-[2-(2-chlorophenyl)ethyl]-1H-imidazol-2-yl] carbonyl]-1-piperidinecarboxylate (interm. 37).

b) A mixture of 9 g of intermediate (1) and 50 ml of hydrobromic acid 48% was stirred for 5 hours at 80° C. The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and dried, yielding 10.85 g (97.5%) of [1-(2-phenylethyl)-1H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide; mp. 275.3° C. (interm. 2).

In a similar manner there was also prepared:
[1-[2-(2-methylphenyl)ethyl]-1H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide hemihydrate; mp. 231.7° C. (interm. 38).

c) A mixture of 55 g of intermediate (2), 70 ml of formaldehyde and 70 ml of formic acid was stirred for 5 hours at reflux temperature. After cooling, the reaction mixture was diluted with Water and basified with NaOH(aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 90:10). The eluent of the desired fraction was evaporated and the residue was dried, yielding 30 g (82.0%) of (1-methyl-4-piperidinyl) [1-(2-phenylethyl)-1H-imidazol-2-yl]methanone (interm. 3).

In a similar manner there were also prepared:
[1-[2-(4-fluorophenyl)ethyl]-1H-imidazol-2-yl](1-methyl-4 -piperidinyl)methanone (interm. 4); and
[1-[2-(2-chlorophenyl)ethyl]-1H-imidazol-2-yl](1-methyl-4 -piperidinyl)methanone (interm. 39).

Example 2

A mixture of 70.6 g of intermediate (2) and 700 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 54 g (75.7 %) of α-[1-(2-phenylethyl)- 1 H-imidazol-2-yl]-4-piperidinemethanol; mp. 144.6° C. (interm. 5).

Example 3

a) A mixture of 28.9 g of 2-(4-methylphenyl)ethanol methanesulfonate, 18.6 g of 1H-imidazole, 22.7 g of potassium carbonate and 600 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was evaporated and the residue was taken up in water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was destilled (13.3 Pa; 120 ° C.), yielding 20.1 g (83.0%) of 1-[2-(4-methylphenyl)ethyl]-1H-imidazole (interm. 6).

In a similar manner there were also prepared:

1-[2-(3-methylphenyl)ethyl]-1H-imidazole; bp. 120° C. at 13.3 Pa (interm. 7), 1-[2-(4-bromophenyl)ethyl] -1H-imidazole (interm. 8), and 1-[2-(3-chlorophenyl)ethyl]-1H-imidazole; bp. 134° C. at 13.3 Pa (interm. 9).

b) A mixture of 67 g of 1-(2-chloroethyl)-3-methoxybenzene, 53.1 g of 1H-imidazole, 99 g of sodium carbonate, 500 ml of 4-methyl-2-pentanone and a few crystals of potassium iodide was stirred for 48 hours at reflux temperature. After cooling, the reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was destilled (13.3 Pa; 160° C.), yielding 49.5 g (62.8%) of 1-[2-(3-methoxyphenyl)ethyl]-1H-imidazole (interm. 10).

Example 4

a) To a stirred amount of 250 ml of N,N-dimethylformamide under nitrogen, there were added portionwise 6 g of a dispersion of sodium hydride in mineral oil and 82.1 g of 4-methylimidazole and then dropwise 132 g of phenylxirane. The whole was stirred for 50 hours and then diluted with 1000 ml of water. The precipitate was filtered off, washed with water and 2,2'-oxybispropane and recrystallized from a mixture of acetonitrile and ethanol. The product was filtered off and dried, yielding 58.1 parts (28.7%) of 5-methyl-α-phenyl-1 H-imidazole-1-ethanol; mp. 192.7° C. (interm. 11).

b) A mixture of 57.1 g of intermediate (11), 130 ml of 2-propanol saturated with HCl and 500 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 5 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was diluted with water and the whole was basified with NaOH(aq.). The product was extracted with dichloromethane and the extracted was dried, filtered and evaporated. The residue was co-evaporated with methylbenzene (3x), yielding 52.9 g (100%) of 5-methyl-1-(2-phenylethyl)-1 H-imidazole (interm. 12).

In a similar manner there was also prepared:

1-[2-(2-methylphenyl)ethyl]-1H-imidazole (interm. 49).

Example 5

a) To a cooled mixture (ice-bath) of 10.1 g of intermediate (10), 12 g of N,N-diethylethanamine and 150 ml of acetonitrile there were added dropwise 21.95 g of ethyl 4-chlorocarbonyl-1-piperidinecarboxylate, keeping the temperature below 20° C. After stirring for 2 hours at room temperature and 4 hours at reflux temperature, there were added dropwise 10 ml NaOH. The whole was refluxed for ½ hour, cooled and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 22 g (100%) of ethyl 4-[[1-[2-(3-methoxyphenyl)ethyl]-1 H-imidazol-2-yl]-carbonyl] -1-piperidinecarboxylate (interm. 13).

In a similar manner there were also prepared:

ethyl 4-[[1-[2-(3-chlorophenyl)ethyl]-1 H-imidazol-2-yl]carbonyl] -piperidinecarboxylate (interm. 14),

1-acetyl-4-[[1-[2-(4-methylphenyl)ethyl]-1 H-imidazol-2-yl]carbonyl] piperidine (interm. 15),

ethyl 4-[[5-methyl-1-(2-phenylethyl)-1 H-imidazol-2-yl]carbonyl]-1 -piperidinecarboxylate (interm. 16),

ethyl 4-[[1-[2-(3-methylphenyl)ethyl]-1 H-imidazol-2-yl]carbonyl]-1 -piperidinecarboxylate (interm. 17),

ethyl 4-[[1-[2-(4-bromophenyl)ethyl]-1 H-imidazol-2-yl]carbonyl] -1-piperidinecarboxylate (interm. 18), and

ethyl 4-[[1-[2-(2-methylphenyl)ethyl]-1 H-imidazol-2-yl]carbonyl]-1 -piperidinecarboxylate (interm. 40).

b) A mixture of 4.4 g of intermediate (13) and 120 ml of hydrochloric acid 12N was stirred for 72 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water, basified with NaOH and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated, yielding 2.63 g (83.9 %) of [1-[2-(3-methoxyphenyl)ethyl]- 1 H-imidazol-2-yl](4-piperidinyl)methanone (interm. 19).

In a similar manner there were also prepared:

1-[2-(4-methylphenyl)ethyl]-1 H-imidazol-2-yl](4-piperidinyl)methanone dihydrochloride (interm. 20),

[1-[2-(3-chlorophenyl)ethyl]-1 H-imidazol-2-yl](4-piperidinyl)methanone (interm. 21), and

[1-[2-(2-methylphenyl)ethyl]-1 H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide; mp. 268.1° C. (interm. 41).

c) A mixture of 130 g of intermediate (16) and 1000 ml of hydrobromic acid 48% was stirred for 24 hours at 80° C. The reaction mixture was evaporated and the residue was recrystallized from 2-propanol. After cooling, the precipitate was filtered off and dried, yielding 124.2 g (95.6%) of [5-methyl-1-(2-phenylethyl)-1H-imidazol-2 -yl](4-piperidinyl dihydrobromide (interm. 22).

In a similar manner there were also prepared:

[1-[2-(3-methylphenyl)ethyl]-1

H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide (interm. 23), and

[1-[2-(4-bromophenyl)ethyl]-1 H-imidazol-2-yl](4-piperidinyl)methanone dihydrobromide hemihydrate (interm. 24).

Example 6

A mixture of 5.24 g of intermediate (24), 2 g of polyoxymethylene, 3 g of potassium acetate, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was taken up in water and the whole was basified with K_2CO_3. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated, yielding 3.2 g (85.0%) of [1-[2-(4-bromophenyl)ethyl]-1 H-imidazol-2-yl](1-methyl-4 -piperidinyl) (interm. 25).

In a similar manner there were also prepared:

[1-[2-(3-chlorophenyl)ethyl]-1 H-imidazol-2-yl](1-methyl-4 -piperidinyl)methanone (interm. 26), and

[1-[2-(3-methoxyphenyl)ethyl]-1 H-imidazol-2-yl](1-methyl-4 -piperidinyl)methanone (interm. 27).

Example 7

a) A mixture of 3.16 g of 1H-3-benzazepin-2-amine, 4.17 g of 2,2-dimethoxyethanamine and 50 ml of methanol was stirred for 16 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in hexane. The precipitate was filtered off, yielding 4.9 g (100%) of N-(2,2-dimethoxyethyl)-1 H-3-benzazepin-2-amine (interm. 28).

b) A mixture of 4.9 g of intermediate (28), 70 ml of acetic acid and 9 ml of hydrochloric acid 36% was stirred for 18 hours at 70° C. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH(aq.) and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was treated with active charcoal in 1,1'-oxybisethane. The whole was filtered and the filtrate was evaporated. The residue was triturated in hexane. The product was filtered off and dried, yielding 1.04 g (28.5%) of 11 H-imidazo[2,1-b][3]benzazepine; mp. 85.5° C. (interm. 29).

c) A mixture of 5 g of intermediate (29), 20 g of manganese dioxide and 150 ml of trichloromethane was stirred for 50 hours at reflux temperature. The whole was filtered over diatomaceous earth, 20 g of manganese dioxide were added and refluxing was continued for 48 hours (2x). The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was triturated in 1,1'-oxybisethane and then boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.61 g (53.2%) of 11 H-imidazo-[2,1-b][3]benzazepin- 11-one; mp. 218.9° C. (interm. 30).

d) A mixture of 10 ml of tetrahydrofuran and 1.24 g of magnesium was stirred under a nitrogen atmosphere. 1 Crystal of iodine and then dropwise 1.2 g of bromoethane were added and at reflux temperature there was added a solution of 6.7 g of 4-chloro-1-methylpiperidine in 25 ml of tetrahydrofuran. After refluxing for 1 hour, the reaction mixture was cooled (0° C.). Then there were added 25 ml of tetrahydrofuran and portionwise 9.8 parts of intermediate (30), keeping the temperature below 10° C. The whole was stirred for 1 hour at room temperature and decomposed with NH_4Cl (aq.). The product was extracted with trichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH (NH_3) 95:5). The eluent of the second fraction was evaporated and the residue was crystallized from acetonitrile in 2 fractions, yielding 4.76 parts (32.2%) of 11-(1-methyl-4-piperidinyl)-11 H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 155.2° C. (interm. 31).

Example 8

Following the procedure of example 10 (c) and (d) 2-phenyl-11H-imidazo[2,1-b][3] benzazepine-11-one was converted into 11-(1-methyl-4-piperidinyl)-2-phenyl-11 H-imidazo[2,1-b][3]benzazepin-11-ol; mp. 239.8° C. (interm. 32).

A mixture of 6 g of intermediate (32) and 300 ml of methanol was hydrogenated at normal pressure and at room temperature in the presence of 3 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 3.2 g (53.5%) of 6,11-dihydro-11-(1-methyl-4-piperidinyl)-2-phenyl-5H-imidazo[2,1-b] [3]benzazepin- 11-ol; mp. 225.3° C. (interm. 33).

Example 9

a) To a cooled (0° C.) mixture of 46.2 g of 3-fluorobenzenethanol, 40 ml of N,N-diethylethanamine and 500 ml of dichloromethane, there were added dropwise 41.2 g of methanesulfonyl chloride, keeping the temperature below 5° C. After stirring for 18 hours at room temperature, the reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 81 g (100%) of 2-(3-fluorophenyl)ethanol methanesulfonate (ester) (interm. 34).

b) A mixture of 72 g of intermediate (34), 45 g of 1 H-imidazole, 55.5 g of potassium carbonate and 1000 ml of tetrahydrofuran was stirred over weekend at reflux temperature. The reaction mixture was filtered over diatomaceous earth and the filtrate was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was distilled (53.2 Pa; 130° C.), yielding 37.8 parts (60.2%) of 1-[2-(3-fluorophenyl)ethyl]-1H-imidazole (interm. 35).

c) To a cooled (−70° C.) mixture of 5.5 g of 2-methyl-N-(1-methylethyl)ethanamine and 100 ml of tetrahy-

drofuran under a nitrogen atmosphere there were added dropwise 22 ml of butyllithium and after stirring for 15 min. at –40° C., 9.5 g of intermediate (35) at –70° C. Stirring at –70° C. was continued for 1 hour and then there were added 9.4 g of ethyl 1-methyl-4-piperidinecarboxylate. The whole was stirred for 18 hours at room temperature, decomposed with water and evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3 OH 95:5→ CH_2Cl_2/CH_3OH 80:20). The eluent of the desired fraction was evaporated, yielding 8 g (50.7%) of [1-[2-(3-fluorophenyl)ethyl]-1H-imidazol-2-yl] (1-methyl-4-piperidinyl)methanone (interm. 36).

Example 10

a) To a stirred and cooled (–70° C.) mixture of 18.8 g of N-(1-methylethyl)-2-propanamine in 200 ml of tetrahydrofuran (under nitrogen atmosphere) were added portionwise 42 ml of butyllithium 2.5M in hexane. The mixture was brought to –40° C. and stirred at this temperature for 15 minutes. The mixture was cooled again to –70° C. and a solution of 17 g of 1-(diethoxymethyl)-1H-imidazole in tetrahydrofuran was added dropwise at this temperature. Stirring was continued for 1 hour and a solution of 18.8 g of ethyl 1-methyl-4-piperidinecarboxylate in 200 ml of tetrahydrofuran was added. After stirring for 1 hour at –70° C. and for another hour at room temperature, the mixture was decomposed with water, acidified with HCl and evaporated. The residue was taken up in water, alkalized with potassium carbonate and extracted with a mixture of dichloromethane and methanol. The extract was dried, filtered and evaporated. The residue was purified on silica (eluent: $CH_2Cl_2/(CH_3OH/NH_3)$95/5). The pure fractions were collected and the eluent was evaporated. The residue was crystallized from acetonitrile. The product was filtered off and dried, yielding: 2.75 g of (1H-imidazol-2-yl)(1-methyl-4-piperidinyl)methanone (12.9%); mp. 143.6° C. (interm. 42).

b) To 200 ml of N,N-dimethylformamide were added portionwise 13.2 g of a sodium hydride dispersion 50% in mineral oil and then 48.3 g of intermediate (42) under nitrogen atmosphere while stirring. After stirring for 1.5 hours at room temperature, a solution of 65 g of 2-fluorobenzeneethanol methanesulfonate (ester) in N,N-dimethylormamide was added dropwise to the reaction mixture. The reaction mixture was stirred for 18 hours at 60° C., cooled and decomposed with water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was taken up in water, acidified with hydrochloric acid, washed twice with 2,2'-oxybispropane, treated with potassium carbonate and extracted again with dichloromethane. The extract was dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate salt in ethanol. The salt was filtered off and dried, yielding 61.9 g (50.6%) of [1-[2-(2-fluorophenyl)ethyl]-1H-imidazol-2-yl](1-methyl- 4-piperidinyl)methanone (E)-2-butenedioate (2:3); mp. 131.7° C. (interm. 43).

Example 11

22.3 g of methyl 4'-methyl-(1,1'biphenyl)-2-carboxylate were dissolved in 900 ml of tetrachloromethane under a nitrogen flow. Then there were added 17.8 g of 1-bromo-2,5-pyrrolidinedione and a catalytic amount of dibenzoyl peroxide. After stirring for 2.5 hours at reflux temperature under a nitrogen atmosphere, the reaction mixture was cooled and filtered. The filtrate was evaporated, yielding >30 g (100%) of methyl 4'-(bromomethyl)[1,1'-biphenyl]-2-carboxylate as a crude residue (interm. 44).

Example 12

a) To a freshly prepared sodium methoxide solution, prepared in the usual manner starting from 23 g of sodium and 350 ml of methanol was added a solution of 68 g of 1H-imidazole in 100 ml of methanol. The solvent was evaporated and the residue was taken up in 320 ml of N,N-dimethylformamide. The solvent was removed again till the temperature rose to 125° C. After cooling to 30° C., 185 g of (2-bromoethyl-)benzene were added to the residue and the whole was stirred overnight. The reaction mixture was diluted with 1500 ml of water and 230 ml of benzene. The separated aqueous layer was extracted twice with benzene. The combined organic layers were treated with 750 ml of a hydrochloric acid solution 4N and than basified. The product was extracted with benzene. The extract was dried, filtered and evaporated. The oily residue was distilled in vacuo, yielding 55 g of 1-(2-phenylethyl)-1 H-imidazole; bp. 140°–145° C. at 23.3 Pa (interm. 45).

b) A mixture of 34.5 g of intermediate (45) and 200 ml of formaldehyde 37% in water was stirred and refluxed for 48 hours. After evaporation, the residue was taken up in water and treated with a diluted ammonium hydroxide solution while cooling. The whole was stirred for 30 minutes and extracted with methylbenzene. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (eluent: CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitated product was filtered off and dried in vacuo, yielding 29.9 g (73.8%) of 1-(2-phenylethyl)-1 H-imidazole-2-methanol; mp. 75.4° C. (interm. 46).

c) To 50 ml of thionyl chloride were added portionwise 4 g of intermediate (46). The reaction mixture was stirred and refluxed for 30 minutes. The reaction mixture was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitated product was filtered off and dried, yielding 4.61 g (89.6%) of 2-(chloromethyl)-1-(2 -phenylethyl)-1H-imidazole monohydrochloride; mp. 240.2° C. (interm. 47).

d) A mixture of 19.6 g of intermediate 47, 59 g of aluminium chloride and 25.5 g of sodium chloride was stirred for 30 minutes at 100° C. After cooling, the reaction mixture was poured into ice water and treated with sodium hydroxide. The product was extracted with methylbenzene. The extract was dried, filtered and evaporated, yielding 13.1 g (93.5%) of 6,11-dihydro-5 H-imidazo[2,1-b][3]benzazepine (interm. 48).

B. Preparation of the final compounds

Example 13

A mixture of 2.5 g of intermediate (26) and 10 ml of trifluoromethanesulfonic acid was stirred for 72 hours at 110° C. under nitrogen. After cooling, the reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichlo-

romethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH (NH_3) 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.95 g (40.4%) of 8-chloro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine; mp. 186.6° C. (comp. 3.10).

Example 14

A mixture of 2 g of intermediate (27) and 10 ml of methanesulfonic acid was stirred for 1 hour at 100° C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 1 g (30.8%) of 6,11-dihydro- 8-methoxy-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 190.3° C. (comp. 3.01).

Example 15

A mixture of 8 g of intermediate (36), 24 g of aluminum chloride and 10.3 g of sodium chloride was stirred at 140° C. until the whole was melted. Stirring was continued for 1 hour at 120° C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was triturated in 2,2'-oxybispropane and recrystallized from 4-methyl-2-pentanone. The product was filtered off and dried, yielding 0.58 g (10.8%) of 8-fluoro-6,11-dihydro-11-(1-methyl- 4-piperidinylidene)-5 H-imidazo[2,1-b][3]benzazepine; mp. 152.4° C. (comp. 3.15).

Example 16

A mixture of 3.5 g of intermediate (5) and 10 ml of trifluoromethanesulfonic acid was stirred for 18 hours at 110° C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was washed with water, dried, filtered and evaporated. The residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was recrystallized from ethanol, yielding 0.8 g (13.3%) of 6,11-dihydro-11-(4-piperidinyl)-5H-imidazo-[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 220.2° C. (comp. 5.01).

Example 17

A mixture of 2.2 g of intermediate (33), 10 ml of sulfuric acid and 10 ml of methanesulfonic acid was stirred for 2 hours at 70° C. The reaction mixture was poured into ice-water and the whole was basified with NaOH (aq.). The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue-was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.73 g (34.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-2-phenyl-5H-imidazo-[2,1-b][3] benzazepine; mp. 171.5° C. (comp. 4.01).

Example 18

A mixture of 14.7 g of intermediate (31) and 150 ml of acetic anhydride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the first fraction was evaporated and the residue was taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was treated with activated charcoal. After filtration, the solution was evaporated and the residue was triturated in 2,2'-oxybispropane. The product was filtered off and dried, yielding 1.6 g (11.5%) of product. The second fraction was also evaporated and the residue taken up in 1,1'-oxybisethane. The whole was filtered and the filtrate was combined with the 2,2'-oxybispropane-filtrate of the first fraction, and evaporated, yielding an additional 8.2 g (59.1%) of product. Total yield: 9.8 g (70.6%) of 11-(1-methyl-4 -piperidinylidene)-11 H-imidazo[2,1-b][3]benzazepine; mp. 135.8° C. (comp. 6.01).

Example 19

To a stirred and refluxing mixture of 7.2 g of compound (3.10), 4.6 g of N,N-diethylethanamine and 200 ml of methylbenzene there were added dropwise 12.5 g of ethyl chloroformate. After refluxing for 1 hour and subsequent cooling, the reaction mixture was diluted with water. The whole was basified with K_2CO_3 and then extracted with methylbenzene. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 6.62 g (77.4%) of ethyl 4-(8-chloro- 5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine-carboxylate; mp. 140.3° C. (comp. 3.11).

Example 20

a) A mixture of 2.5 g of compound (1.03) and 50 ml of formaldehyde 40% was stirred for 1 week at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NH_4OH, stirred for ½ hour and extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 0.45 g (16.3%) of ethyl 4-[5,6-dihydro-3-(hydroxymethyl)-11H-imidazo[2,1-b][3]benzazepin-11-ylidene]-1-piperidinecarboxylate; mp. 191.9° C. (comp. 4.11).

b) A mixture of 20 g of compound (1.03) and 400 ml of formaldehyde 40% was stirred for 2 weeks at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NH_4OH, the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the third fraction was evaporated, yielding 4.1 g (17.2%) of ethyl 4-[5,6-dihydro-2,3-bis(hydroxymethyl)-I 1H-imidazo-[2,1-b][3] -benzazepin-11-ylidene]-1-piperidinecarboxylate (comp. 4.18).

Example 21

A mixture of 13 g of compound (1.03), 13 g of potassium

hydroxide and 100 ml of 2-propanol was stirred for 6 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in ethanol. The salt was filtered off and dried, yielding 3.52 g (18.3%) of 6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2) hemihydrate; mp. 192.5° C. (comp. 1.04).

Example 22

A mixture of 60 g of compound (6.02) and 500 ml of hydrobromic acid 48% was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. After basifying with NaOH (aq.), the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the first fraction was evaporated and the residue was converted into the dihydrobromide salt in ethanol. The salt was filtered off and dried, yielding 27.3 g (37.7%) of 11-(4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepine dihydrobromide hemihydrate; mp. 246.9° C. (comp. 6.03).

Example 23

A mixture of 6.1 g of compound (3.11) and 100 ml of hydrochloric acid 12N was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was boiled in 2-propanol. After cooling, the precipitate was filtered off and taken up in water. The whole was basified with NaOH (aq.) and then extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was boiled in acetonitrile. After cooling, the product was filtered off and dried, yielding 2.9 g (59.0%) of 8-chloro-6,11-dihydro-11-(4-piperidinylidene)-5H-imidazo[2,1-b]-[3]benzazepine; mp. 197.1° C. (comp. 3.12).

Example 24

To a stirred and cooled (ice-bath) mixture of 5.6 g of compound (2.12), 50 ml of dichloromethane and 2.5 g of N,N-diethylethanamine there was added dropwise a solution of 2.38 g of ethyl chloroformate in 20 ml of dichloromethane. Stirring was continued for 1 hour at room temperature. The reaction mixture was diluted with water and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 2.85 g (40.5%) of ethyl 4-(5,6-dihydro-9-methyl-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinecarboxylate; mp. 156.5° C. (comp. 2.13).

Example 25

A mixture of 1.79 g of 3-(2-chloroethyl)-2-oxazolidinone, 2.65 g of compound (1.04), 1.3 g of sodium carbonate, 150 ml of 4-methyl-2-pentanone and 1 g of potassium iodide was stirred for 18 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The aqueous layer was separated and extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (2:3) salt in ethanol. The salt was filtered off and dried, yielding 3.4 g (61.5%) of 3-[2-[4-[5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene]-1-piperidinyl] ethyl]-2-oxazolidinone (E)-2-butenedioate (2:3); mp. 188.8° C. (comp. 1.20).

Example 26

A mixture of 2.3 g of 6-(2-chloroethyl)-7-methylthiazolo [3,2-a]pyrimidin-5-one, 2.65 g of compound (1.04), 1.3 g of sodium carbonate and 100 ml of 4-methyl-2-pentanone was stirred for 24 hours at reflux temperature. After cooling, the reaction mixture was diluted with water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 1.89 g (41.3%) of 6-[2-[4-(5,6-dihydro- 11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one; mp. 181.8° C. (comp. 1.13).

Example 27

A mixture of 0.83 g of chloroacetonitrile, 2.65 g of compound (1.04), 1.1 g of N,N-diethylethanamine and 80 ml of N,N-dimethylacetamide was stirred for 18 hours at room temperature. The reaction mixture was poured into water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.0 g (65.7%) of 4-(5,6-dihydro-11H-imidazo[2,1-b][3] -benzazepin-11-ylidene)- 1-piperidineacetonitrile; mp. 220.4° C. (comp. 1.26).

Example 28

A mixture of 1.0 g of 3-chloro-2-methyl-1-propene, 2.6 g of compound (1.04), 1.6 g of sodium carbonate and 50 ml of N,N-dimethylacetamide was stirred for 20 hours at 50° C. After cooling, there were added 100 ml of ethyl acetate. The whole was washed with water (3x), dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butene-dioate (2:3) salt in 2-propanol. The salt was filtered off and dried, yielding 2.8 g (56.7%) of 6,11-dihydro- 11-[1-(2-methyl-2-propenyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (2:3); mp. 179.5° C. (comp. 1.08).

Example 29

A mixture of 1.57 g of 4-chloro-2-methyl-2-butene (dissolved in N,N-dimethylformamide), 2.65 g of compound (1.04), 1.1 g of sodium carbonate, 0.01 g of potassium iodide and 100 ml of N,N-dimethylacetamide was stirred for 18 hours at room temperature. The reaction mixture was poured into water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified twice by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH(NH_3)$ 90:10:1; HPLC; Lichroprep RP18; CH_3COONH_4 in H_2O 0.5% /CH_3OH /CH_3CN 40:55:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.25 g (7.5%) of 6,11-dihydro-11-[1-(3-methyl-2-butenyl)-4-piperidinylidene]-5H-imidazo[2,1-b][3]benzazepine; mp. 127.2° C. (comp. 1.09).

Example 30

A mixture of 19 g of compound (2.03), 6 g of chloroacetonitrile, 8 g of N,N-diethylethanamine and 100 ml of N,N-dimethylformamide was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted

with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 4.15 g (19.2%) of 4-(9-fluoro-5,6-dihydro-11H-imidazo[2,1-b][3]-benzazepin- 11-ylidene)-1-piperidineacetonitrile; mp. 198.3° C. (comp. 2.08).

Example 31

To a stirred mixture of 2.83 g of compound (2.03), 2.12 g of sodium carbonate, 50 ml of N,N-dimethylformamide and 1 g of potassium iodide there were added dropwise 25.4 g of 4-chloro-2-methyl-2-butene (dissolved in N,N-dimethyl-formamide). Stirring at room temperature was continued for 50 hours. The reaction mixture was diluted with water and extracted with 4-methyl-2-pentanone. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.65 g (45.4%) of 9-fluoro-6,11-dihydro-11-[1-(3-methyl-2 -butenyl)-4-piperidinylidene]-5H-imidazo-[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 203.4° C. (comp. 2.04).

Example 32

A mixture of 1.5 g of 3-bromo-1-propene, 2.65 g of compound (1.04), 1.0 g of sodium hydrogen carbonate and 100 ml of ethanol was stirred for 5 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with 4-methyl-2-pentanone and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH(NH_3)$ 90:10:0→90:10:1). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butene-dioate (1:2) salt in 2-propanone. The salt was filtered off and dried for 2 hours in vacuo at 100° C., yielding 1.1 g (20.5%) of 6,11-dihydro-11-[1-(2-propenyl)-4-piperidinylidene] -5H-imidazo-[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 160.8° C. (comp. 1.07).

Example 33

A mixture of 2.7 g of compound (3.04), 1 g of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and 50° C. in the presence of 1 g of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH(NH_3)$ 95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate (1:2) salt in 2-propanol. The salt was filtered off and dried, yielding 3.1 g (59.0%) of 6,11-dihydro-8-methyl-11 -(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine (E)-2-butenedioate (1:2); mp. 211.0° C. (comp. 3.05).

Example 34

A mixture of 2.7 g of compound (5.01), 2 g of polyoxymethylene, 2 ml of a solution of thiophene in methanol 4% and 150 ml of methanol was hydrogenated at normal pressure and room temperature in the presence of 2 g of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was partitioned between dichloromethane and NH_4OH. The aqueous layer was separated and re-extracted with dichloromethane. The combined organic layers were dried, filtered and evaporated. The residue was crystallized from a mixture of 2,2'-oxybispropane and acetonitrile (2x). The product was filtered off and dried, yielding 0.76 g (26.2%) of 6,11-dihydro-11-(1-methyl-4-piperidinyl)- 5H-imidazo-[2,1-b][3]benzazepine hemihydrate; mp. 117.8° C. (comp. 5.02).

Example 35

A mixture of 2.65 g of compound (1.04), 20 ml of acetic acid and 15 ml of 2-propanone was stirred for 2 hours at room temperature under nitrogen. There were added portionwise 1.5 g of sodium tetrahydroborate and stirring was continued for 18 hours. The reaction mixture was diluted with water and basified with NaOH 15%. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH(NH_3)$ 90:10:1). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate (1:2) salt in 2-propanone. The salt was filtered off and dried, yielding 2.5 g (46.3%) of 6,11-dihydro-11-[1-(1-methyl-ethyl)-4 -piperidinylidene]- 5H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate (1:2); mp. 183.6° C. (comp. 1.06).

Example 36

A mixture of 4 g of compound (4.03), 2 ml of acetic acid, 3 g of sodium acetate and 20 ml of formaldehyde 37% was stirred for 50 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The whole was basified with NaOH (aq.) and extracted with a mixture of dichloromethane and methanol. The extract was dried, filtered and evaporated and the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5→$CH_2Cl_2/CH_3OH(NH_3)$ 90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of acetonitrile and 2,2'-oxybispropane. The product was filtered off and dried, yielding 0.4 g (9.2%) of 6,11-dihydro-3-methyl-11-(1-methyl-4-piperidinylidene)- 5H-imidazo-[2,1-b][3]benzazepine-2-methanol; mp. 166.8° C. (comp. 4.21).

Example 37

A mixture of 1.6 g of (2-pyridinyl)ethene, 2.7 g of compound (5.01) and 100 ml of 1-butanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH:NH_3$ 90:10:1). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 1.7 g (45.6%) of 6,11-dihydro-11-[1-[2-(2-pyridinyl)ethyl]- 4-piperidinyl]- 5H-imidazo-[2,1-b][3]benzazepine; mp. 170.3° C. (comp. 5.04).

Example 38

Through a stirred mixture of 32 g of compound (1.04) and 300 ml of methanol was bubbled gaseous oxirane for 1 hour at room temperature. After stirring for 3 hours at room temperature, the mixture was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH:NH_3$ 90:10:0→90:10:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in acetonitrile. The salt was filtered off and dried, yielding 15 g (23.1%)of 4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidineethanol (Z)-2-butenedioate(1:2); mp. 145.7° C. (comp. 1.30).

Example 39

A solution of 9.6 g of compound (4.08) in 300 ml of methanol/NH_3 was hydrogenated in the presence of 3 g of

Raney Nickel catalyst. After complete reaction, the catalyst was filtered off and the filtrate was evaporated, yielding 12.5 g (100%) of 4-(5,6-dihydro-3 -methyl-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1- piperidineethanamine (comp. 4.09).

Example 40

0.57 g of lithium aluminum hydride were added portionwise to 100 ml of tetrahydrofuran under nitrogen. A solution of 2.3 g of compound (1.26) in tetrahydrofuran was added dropwise and the reaction mixture was stirred for 3 hours at reflux temperature. The mixture was decomposed with 2 ml of water, 2 ml of a sodium hydroxide solution 15%. After filtration over diatomaceous earth, the filtrate was evaporated, yielding 2.3 g (97.5%) of 4-(5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin-11-yl)-1 -piperidineethanamine (comp. 5.07).

Example 41

A solution of 3.1 g of compound (1.30) in N,N-dimethylacetamide was added dropwise to a mixture of 0.7 g of a sodium hydride dispersion 50% and 200 ml of N,N-dimethylacetamide under nitrogen and at room temperature. After stirring for 1 hour, 1.1 g of 2-chloropyrimidine were added and the whole was stirred for 16 hours at room temperature. The reaction mixture was decomposed with water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 1.4 g (22.6%) of 6,11-dihydro-11-[1-[2-(2-pyrimidinyloxy)ethyl]-4-piperidinylidene]- 5 H-imidazo[2,1-b][3]benzazepine (Z)-2-butenedioate(1:2); mp. 172.6° C. (comp. 1.31).

Example 42

A mixture of 3.3 g of 2-chloropyrimidine, 3.2 g of compound (4.09), 1.26 g of sodium hydrogen carbonate and 200 ml of ethanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH95:5→90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile. The product was filtered off and dried, yielding 2.56 g (63.9%) of N-[2-[4-(5,6-dihydro-3-methyl-11H-imidazo[2,1-b] [3]benzazepin-11-ylidene)- 1-piperidinyl]ethyl]-2-pyrimidinamine; mp. 171.3° C. (comp. 4.10).

Example 43

A mixture of 2.0 g of 5-bromo-1,3,4-thiadiazole-2-amine, 3.42 g of compound (1.27), 1.2 g of sodium carbonate, 0.01 g of potassium iodide and 200 ml of N,N-dimethylacetamide was stirred for 4 hours at 120° C. The reaction mixture was evaporated and the residue was stirred in dichloromethane. The organic layer was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH:NH_3$90:10:1→90:7:3). The eluent of the desired fraction was evaporated and the residue was crystallized from a mixture of acetonitrile and ethanol. The product was filtered off and dried, yielding 1.62 g (36.2%) of N^2-[2-[4-(5,6 -dihydro-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1- piperidinyl] ethyl]-1,3,4 -thiadiazole-2,5-diamine; mp. 251.4° C. (comp. 1.33).

Example 44

To a stirred mixture of 1.1 g of 3-furancarboxylic acid, 1.9 g of N,N-diethylethanamine and 200 ml of dichloromethane were added portionwise 2.4 g of 2-chloro-1-methylpyridinium iodide. After stirring for 1 hour at room temperature, a solution of 2.9 parts of compound (1.27) in dichloromethane was added dropwise. Upon completion, the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was basified with K_2CO_3(aq.) and extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 94:6→90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 1.88 g (31.5%) of N-[2-[4-(5,6-dihydro- 11H-imidazo-[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-3-furancarboxamide (Z)-2-butenedioate(1:2); mp. 202.9° C. (comp. 1.35).

Example 45

A mixture of 0.6 g of isocyanatomethane, 3.1 g of compound (1.27) and 100 ml of tetrahydrofuran was stirred for 18 hours at room temperature. The reaction mixture was evaporated and the residue was crystallized from acetonitrile. The precipitated product was filtered off and dried, yielding 2.0 g (54.7%) of N-[2-[4-(5,6-dihydro- 11 H-imidazo-[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]-ethyl]-N'-methylurea; mp. 178.1° C. (comp. 1.36).

Example 46

a) To a stirred and cooled (−10° C.) mixture of 18 g of carbon disulfide, 7.22 g of N,N'-methanetetraylbis[cyclohexanamine]and 150 ml of tetrahydrofuran was added dropwise a solution of 10.8 g of compound (1.27) in tetrahydrofuran. After stirring for 1 hour at room temperature, the reaction mixture was evaporated, yielding 12 g (97.5%) of 6,11-dihydro-11-[1-(2-isothiocyanatoethyl)-4-piperidinylidene]- 5H-imidazo[2,1-b]- 3]benzazepine (comp. 1.37).

b) A mixture of 2.7 g of 3,4-pyridinediamine, 8.8 g of compound (1.37) and 150 ml of tetrahydrofuran was stirred for 18 hours at reflux temperature, yielding 11.5 g (100%) of N-(4-amino- 3-pyridinyl)-N'-[2-[4-(5,6-dihydro- 11 H-imidazo[2,1-b][3]benzazepin- 11-ylidene)-1-piperidinyl]ethyl]thiourea (comp. 1.38).

c) A mixture of 11.5 g of compound (1.38), 7.6 g of mercury(II)oxide, 0.01 g of sulfur and 150 ml of tetrahydrofuran was refluxed for 5 hours. The reaction mixture was filtered while hot over diatomaceous earth and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH:NH_3$ 90:5:5). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate salt in methanol. The salt was filtered off and dried, yielding 1.65 g (14.4%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin- 11-ylidene)-1-piperidinyl]ethyl]-1 H-imidazo[4,5-c]pyridin-2-amine (E)-2-butenedioate(1:3) hemihydrate; mp. 203.0° C. (comp. 1.39).

Example 47

1 g of gaseous methanamine was bubbled through 100 ml of tetrahydrofuran. A solution of 3.5 g of compound (1.37) in tetrahydrofuran was added and the reaction mixture was stirred for 2 hours at room temperature. After evaporation,

the residue was purified by column chromatography (silica gel; $CH_2Cl_2/CH_3OH/CH_3OH:NH_3$ 90:10:0→90:10:1). The eluent of the desired fraction was evaporated and the residue was crystallized from 2,2'-oxybispropane. The crystallized product was filtered off and dried, yielding 0.9 g (23.0%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]ethyl]-N'-methylthiourea hemihydrate; mp. 155.2° C. (comp. 1.40).

Example 48

a) A mixture of 7.6 g of compound (1.30) and 100 ml of thionyl chloride was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was stirred in methylbenzene (2x). The obtained residue was dissolved in water and treated with sodium carbonate. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH95:5). The eluent of the desired fraction was evaporated and the residue was converted into the (Z)-2-butenedioate salt in 2-propanone. The salt was filtered off and dried, yielding 0.7 g (5%) of 11-[1-(2-chloroethyl)-4-piperidinylidene]-6,11-dihydro-5 H-imidazo[2,1-b][3]-benzazepine (Z)-2-butenedioate(1:2); mp. 169.9° C. (comp. 1.41).

b) A mixture of 2.8 g of 1-methyl-1 H-imidazol-2-thiol, 6.5 g of compound (1.41), 8.3 g of potassium carbonate and 200 ml of 2-propanone was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated, the residue was taken up in dichloromethane, washed with water, dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH90:10). The eluent of the desired fraction was evaporated and the residue was taken up in methylbenzene and treated with activated charcoal. The whole was filtered while hot, the filtrate was allowed to cool and was then evaporated. The residue was converted into the cyclohexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 1.6 g (10.5%) of 6,11-dihydro-11-[1-[2-[(1-methyl-1H-imidazol-2 -yl)thio]-ethyl]- 4-piperidinylidene]-5 H-imidazo[2,1-b][3]benzazepine cyclohexanesulfamate (1:2); mp. 265.4° C. (decomp.) (comp. 1.42).

Example 49

a) A mixture of 9.6 g of methyl N-(2,2'-dimethoxyethyl)-N'-methylcarbamimidothioate hydroiodide, 9.3 g of compound (1.27) and 200 ml of 2-propanol was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated, yielding 17.4 g (100%) of N-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b]-[3] benzazepin-11-ylidene)-1-piperidinyl]ethyl]-N'-(2,2-dimethoxyethyl)-N"-methylguanidine monohydroiodide (comp. 1.43).

b) A mixture of 9.3 g of compound (1.43) and 200 ml of a hydrochloric acid solution was stirred for 18 hours at room temperature. The whole was treated with potassium carbonate and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography HPLC (silica gel; $CHCl_3/CH_3OH$98:2). The eluent of the desired fraction was evaporated and the residue was converted into the cyclohexanesulfamate salt in 2-propanone and ethanol. The salt was filtered off and dried, yielding 0.71 g (3%) of 4-(5,6-dihydro- 11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-N-(1-methyl-1H -imidazol-2-yl)-1 -piperidine-ethanamine cyclohexanesulfamate (1:3) dihydrate; mp. 153.9° C. (comp. 1.44).

Example 50

A mixture of 1.42 g of 2-mercapto-4-pyrimidinone, 3.1 g of compound (1.27) and 1 ml of N,N-dimethylacetamide was stirred for 4 hours at 140° C. After cooling, the mixture was purified by column chromatography (silica gel; $CHCl_3/CH_3OH$95:5). The eluent of the desired fraction was evaporated and the residue was converted into the hydrochloride salt in 2-propanone. The salt was filtered off and dried in vacuo, yielding 1.8 g (32.9%) of 2-[[2-[4-(5,6-dihydro-11 H-imidazo-[2,1-b][3]-benzazepin-11-ylidene)-1-piperidinyl]ethyl]amino]-4(1H)-pyrimidinone trihydrochloride dihydrate; mp. 234.8° C. (comp. 1.45).

Example 51

A mixture of 1 g of compound (4.11), 5 g of manganese(IV)oxide and 100 ml of trichloromethane was stirred for 2 hours at reflux temperature. The reaction mixture was filtered while hot over diatomaceous earth. After evaporation, the residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from 1,1'-oxybisethane. The product was filtered off and dried, yielding 0.48 g (48.6%) of ethyl 4-(3-formyl-5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidine mp. 138.2° C. (comp. 4.15).

Example 52

To a stirred solution of 9.7 g of compound (4.15) in 100 ml of water was added dropwise a solution of 13.7 g of $AgNO_3$ in 50 ml of water and then a solution of 13.3 g of potassium hydroxide in 50 ml of water. After stirring for 18 hours, the reaction mixture was filtered and the filtrate acidified with hydrochloric acid. After evaporation, the residue was stirred in methanol, the precipitate was filtered off and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; $NH_4OAc/H_2O/CH_3OH$55:0.5:45). The eluent of the desired fraction was evaporated and the residue was stirred in 2-propanone and activated charcoal. The precipitate was filtered off and the filtrate was evaporated. The residue was crystallized first from 2,2'-oxybispropane and then from acetonitrile. The product was filtered off and dried, yielding 0.3 g (3%) of 11-[1-(ethoxycarbonyl)-4-piperidinylidene]-6,11-dihydro- 5 H-imidazo[2,1-b][3]benzazepine-3-carboxylic acid; mp. 182.2° C. (comp. 4.17).

Example 53

To a stirred mixture of 2.93 g of compound (4.03), 1.3 g of sodium acetate and 30 ml of acetic acid was added dropwise a solution of 1.6 g of bromine in 20 ml of acetic acid. After stirring for 1 hour at 30° C., the mixture was evaporated and the residue was taken up in water. The aqueous solution was treated with sodium hydroxide and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH95:5→$CH_2Cl_2/CH_3OH/CH_3OH:NH_3$90:8:2). The eluent of the desired fraction was evaporated and the residue was boiled in acetonitrile. After cooling, the precipitated product was filtered off and dried, yielding 0.96 g (25.8%) of 2-bromo-6,11-dihydro-3 -methyl-11-(1-methyl-4-piperidinylidene)-5H-imidazo-[2,1-b][3]benzazepine; mp.

116.0° C. (comp. 4.22).

Example 54

a) A mixture of 6.1 g of 6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo-[2,1-b][3]benzazepine-3-carboxaldehyde and 5.3 g of monoethyl ester propanedioic acid in 1 ml of piperidine and 50 ml of pyridine was stirred and refluxed for 4 hours. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane, dried, filtered and evaporated, yielding 13 g (100%) of ethyl 3-[5,6-dihydro-11-(1 -methyl-4-piperidinylidene)- 11 H-imidazo[2,1-b][3]benzazepin-3-yl]-2-propenoate (comp. 4.27).

b) A solution of 1.12 g of potassium hydroxide in 40 ml of water was added dropwise to a stirred mixture of 13 g of compound (4.27) in 20 ml of tetrahydrofuran. The mixture was stirred overnight, acidified with HCl and evaporated. The residue was purified by HPLC Lichroprep 18 25 μm (eluent: NH_4OAc/H_2O/ CH_3CN 0.5/89.5/10 H_2OCH_3CN90/10). The eluent of the desired fraction was evaporated and the residue was stirred in 500 ml of 2-propanone, decolourized with activated charcoal and filtered over diatomaceous earth. The filtrate was evaporated and the residue was stirred in 1,1'-oxybisethane. The product was filtered off and dried, yielding 0.9 g (11.9%) of ethyl (E)-3-[5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b][3]benzazepin-3-yl]-2-propenoic acid sesquihydrate; mp. 207.3° C. (comp. 4.28).

Example 55

a) A mixture of 2.64 g of 2,5-dimethoxytetrahydrofuran, 3.1 g of compound (1.27), 30 ml of water and 10 ml of acetic acid was stirred for 1.5 hours at 50° C. The mixture was basified with NaOH(aq.) and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 95:5). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 1.17 g (33%) of 6,11-dihydro-11-[1-[2-(1H-pyrrol-1-yl)ethyl]-4 -piperidinylidene]-5H-imidazo-[2,1-b][3]benzazepine; mp. 165.5° C. (comp. 1.55).

b) To 60 ml of N,N-dimethylformamide were added dropwise 5.9 g of phosphoryl chloride. After stirring for 30 minutes at room temperature, there was added a solution of 13.7 g of compound (1.55) in N,N-dimethylformamide and stirring at room temperature was continued for 1 hour. The reaction mixture was poured into a mixture of ice, water and potassium carbonate and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 96:4). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 6.4 g (43%) of 1-[2-[4-(5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl] ethyl]-1H-pyrrole-2-carboxaldehyde; mp. 158.5° C. (comp. 1.56).

c) To a cooled mixture (ice-bath) of 4.4 g of compound (1.56) and 100 ml of methanol was added portionwise over 15 minutes 1.1 g of sodium tetrahydroborate. After stirring for 1 hour at room temperature, the reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 97:3 to 93:7). The eluent of the desired fraction was evaporated and the residue was crystallized from acetonitrile, yielding 2.74 g (62%) of 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3]benzazepin-11 -ylidene)-1-piperidinyl]-ethyl] -1 H-pyrrole-2-methanol; mp. 147.4° C. (comp. 1.57).

Example 56

a) A mixture of 4.3 g of compound (1.27), 5.2 g of ethyl 2,5-diethoxy-tetrahydofuran- 2-carboxylate and 100 ml of acetic acid was stirred for 2 hours at 80° C. The mixture was evaporated and the residue was taken up in water. The whole was basified with potassium carbonate and the product extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 96:4→90:10). The eluent of the desired fraction was evaporated and the residue was crystallized from acetontrile, yielding 4.3 g (70%) of ethyl 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3] benzazepin-11-ylidene)-1-piperidinyl] ethyl]-1H-pyrrole-2-carboxylate; mp. 158.5° C. (comp. 1.58).

b) A mixture of 3.2 g of compound (1.58), 40 ml of sodium hydroxide (1N), 50 ml of tetrahydrofuran and 100 ml of water was stirred for 48 hours at reflux temperature. The reaction mixture was evaporated and the residue was washed with dichloromethane. The whole was neutralized with HCl (1N) and the product was extracted with dichloromethane. The organic layer was dried, filtered and evaporated. The product was crystallized successively from 2-propanone and acetonitrile, yielding 1.06 g (36%) of 1-[2-[4-(5,6-dihydro-11H-imidazo[2,1-b][3] benzazepin-11-ylidene)-1-piperidinyl]-ethyl] -1 H-pyrrole-2-carboxylic acid hemihydrate; mp. 166.2° C. (comp. 1.59).

Example 57

To a mixture of 3 g of compound (3.23) and 10 ml of tetrahydrofuran was added dropwise a solution of 0.45 g of potassium hydroxide in 20 ml of water. After stirring overnight at room temperature, the reaction mixture was evaporated and the aqueous layer was washed three times with dichloromethane. The aqueous layer was discoloured with activated charcoal, filtered over diatomaceous earth and concentrated. The aqueous layer was neutralized with HCl till pH=7. The precipitate was filtered off, washed with water and dried, yielding 1.26 g (40%) of 4-(8-fluoro-5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinepropanoic acid dihydrate; mp. 136.1° C. (comp. 3.31).

Example 58

A mixture of 1.9 g of compound (3.28) and 50 ml of hydrobromic acid 48% (aq.) was stirred for 2 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water and basified with potassium carbonate. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was purified by column chromatography (silica gel; CH_2Cl_2/CH_3OH 94:6→90:10). The eluent of the desired fraction was evaporated and the residue was converted into the (E)-2-butenedioate salt (2:3) in 2-propanol; yielding 1.15 g (42%) of 4-[2-[4-(5,6-dihydro-8-methyl-11 H-imidazo[2,1-b][3]benzazepin-11-ylidene)-1-piperidinyl]

-ethyl] phenol hemiethanolate hemihydrate (E)-2-butenedioate(2:3); mp. 176.0° C. (comp. 3.30).

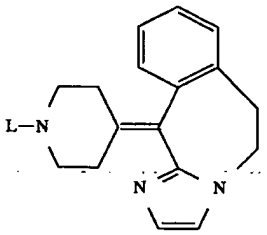
Example 59

a) A mixture of 4.3 g of compound (4.16), 9 g of methyl (methylthio)methanesulfoxide 97%, 50 ml of tetrahydrofuran and 20 ml of a solution of benzyltrimethylammonium hydroxide in methanol 40% was stirred for 18 hours at reflux temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with dichloromethane and the extract was dried, filtered and evaporated. The residue was co-evaporated with methylbenzene (2x) and then taken up in 50 ml of methanol. This solution was cooled on ice and gasueous hydrochloride was bubbled through for ½ hour. After stirring overnight, the whole was evaporated. The residue was taken up in water and basified with potassium carbonate. The product was extracted with dichloromethane and further purified by column chromatography (silica gel; $CH_2Cl_2/C_2H_5OH(NH_3)$ 97:3). The desired fraction was evaporated, yielding 3.15 g (29.9%) of methyl [5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo-[2,1-b][3] benzazepin-3-yl]acetate (comp. 4.30).

b) To a stirred mixture of 3.15 g of compound (4.30) and 10 ml of tetrahydrofuran there was added dropwise a solution of 0.56 g of potassium hydroxide in 20 ml of water. Stirring was continued overnight. The organic solvent was evaporated and the remaining aqueous layer was successively washed with dichloromethane (3x) and stirred with activated charcoal. After filtration, the whole was concentrated and then neutralized to pH 7. The product was filtered off and purified by column chromatography (RP 18; CH_3COONH_4(0.5% in H_2O)/CH_3CN 90:10). The eluent of the desired fraction was evaporated and the residue was recrystallized from acetonitrile, yielding 1.39 g (45.9%) of [5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11H-imidazo[2,1-b] [3]benzazepin-3-yl] acetic acid (comp. 4.31).

All compounds listed in Tables 1–7 were prepared following methods of preparation described in examples 13–59, as is indicated in the column Ex. No.

TABLE 1



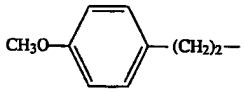
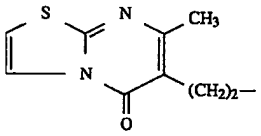
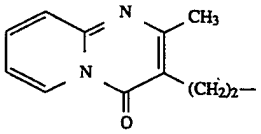
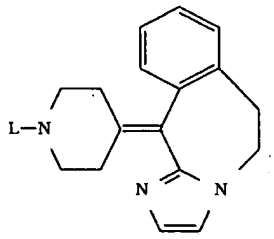
Co. No.	Ex. No.	L—	Physical data
1.01	13	CH_3—	mp. 209.3° C./CF_3SO_3H
1.02	13	CH_3—	mp. 154.5° C.
1.03	19	H_5C_2OOC—	mp. 170.6° C.
1.04	21	H—	mp. 192.5° C./½H_2O.2(E)*
1.05	34	C_2H_5—	mp. 184.2° C./2(Z)*
1.06	35	$CH_3CH(CH_3)$—	mp. 183.6° C./2(Z)*
1.07	32	$CH_2=CH-CH_2$—	mp. 160.8° C./2(Z)*
1.08	28	$CH_2=C(CH_3)-CH_2$—	mp. 179.5° C./3/2(E)*
1.09	29	$CH_3-C(CH_3)=CH-CH_2$—	mp. 127.2° C.
1.10	25	$C_6H_5-CH=CH-CH_2$—	mp. 172.2° C./(E)
1.11	33	$C_6H_5-CH_2$—	mp. 207.2° C.
1.12	26		mp. 180.5° C./2($COOH)_2$
1.13	26		mp. 181.8° C.
1.14	25		mp. 197.8° C./H_2O.3(E)*

TABLE 1-continued



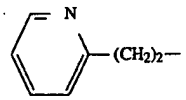
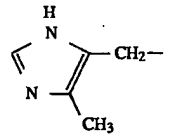
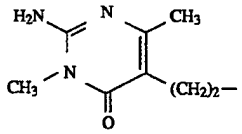
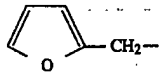
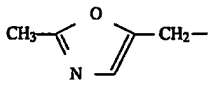
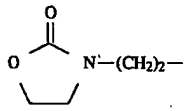
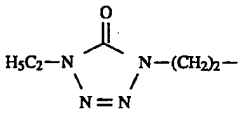
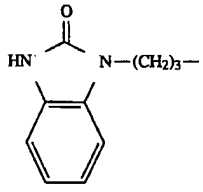
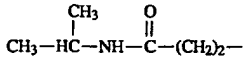
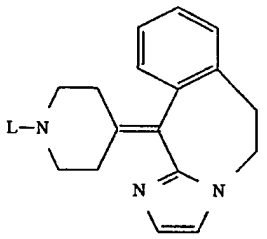
Co. No.	Ex. No.	L—	Physical data
1.15	37		mp. 163.8° C.
1.16	28		mp. 199.0° C.
1.17	25		mp. 257.4° C.
1.18	34		mp. 160.3° C.
1.19	26		mp. 162.1° C./H_2O.2(E)*
1.20	25		mp. 188.8° C./½(E)*
1.21	25		mp. 170.7° C./2(Z)*
1.22	25		mp. 194.7° C.
1.23	25	$C_2H_5-O-(CH_2)_2-$	mp. 176.5° C./2(Z)*
1.24	25		mp. 165.5° C.
1.25	25	$H_5C_2OOC-NH-(CH_2)_2-$	mp. 167.2° C./2(E)*
1.26	27	$NC-CH_2-$	mp. 220.4° C.
1.27	21	$H_2N-(CH_2)_2-$	—

TABLE 1-continued



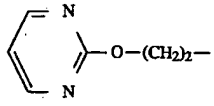
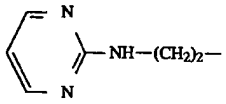
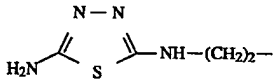
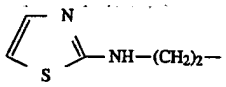
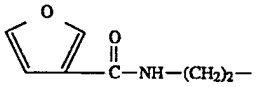
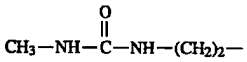
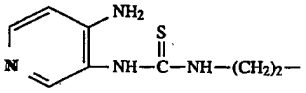
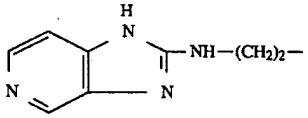
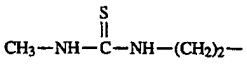
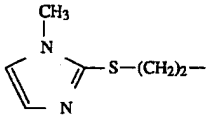
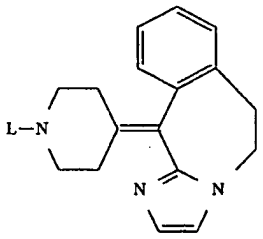
Co. No.	Ex. No.	L—	Physical data
1.28	39	$H_2N-(CH_2)_2-$	mp. 186.6° C./½H_2O.3(E)*
1.29	38	$HO-(CH_2)_2-$	mp. 225.1° C./CF_3SO_3H
1.30	38	$HO-(CH_2)_2-$	mp. 145.7° C./2(Z)*
1.31	41		mp. 172.6° C./2(Z)*
1.32	42		mp. 165.1° C.
1.33	43		mp. 251.4° C.
1.34	43		mp. 205.5° C./½H_2O/4**
1.35	44		mp. 202.9° C./2(Z)*
1.36	45		mp. 178.1° C.
1.37	46a	$SCN-(CH_2)_2-$	
1.38	46b		—
1.39	46c		mp. 203.0° C./½H_2O.3(E)*
1.40	47		mp. 155.2° C./½H_2O
1.41	48	$Cl-(CH_2)_2-$	mp. 169.9° C./2(Z)*
1.42	48		mp. 265.4° C. (dcc.)/2**

TABLE 1-continued



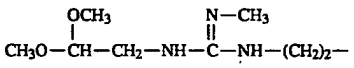
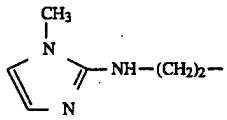
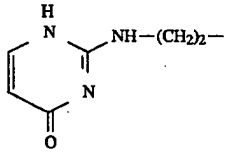
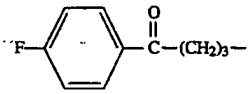
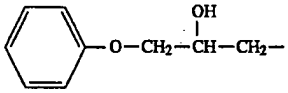
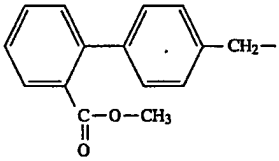
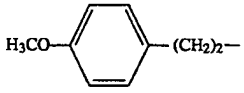
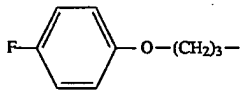
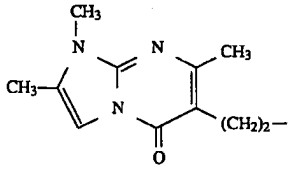
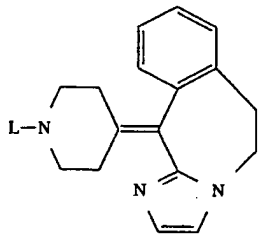
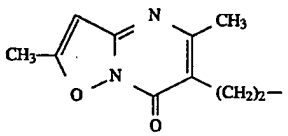
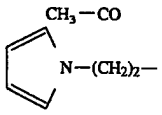
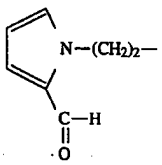
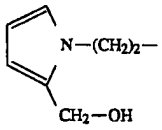
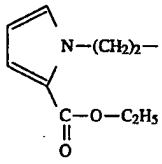
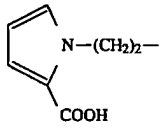
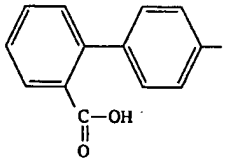
Co. No.	Ex. No.	L—	Physical data
1.43	49a		HI
1.44	49b		mp. 153.9° C./2H_2O.3**
1.45	50		mp. 234.8° C./2H_2O. 3HCl
1.46	26		mp. 161.0° C.
1.47	38		2-(E)*/mp. 156.4° C.
1.48	28	H_5C_2—O—CO—$(CH_2)_2$—	—
1.49	27		mp. 131.5° C.
1.50	27		(E)*.1/2H_2O.1/2ethanolate/ mp. 127.4° C.
1.51	25		mp. 130.3° C.
1.52	25		mp. 195.9° C.

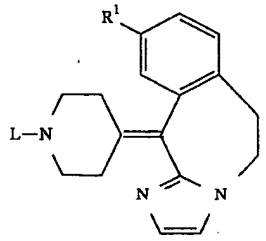
TABLE 1-continued



Co. No.	Ex. No.	L—	Physical data
1.53	25		mp. 202.9° C.
1.54	24		mp. 182.1° C.
1.55	55a		mp. 165.5° C.
1.56	55b		mp. 158.5° C.
1.57	55c		mp. 147.4° C.
1.58	56a		mp. 158.5° C.
1.59	56b		½H_2O/mp. 166.2° C.
1.60	57	HOOC—$(CH_2)_2$—	2 H_2O/mp. 154.9° C.
1.61	57		ethanolate(1:1) mp. 208.6° C.

*: 2-butenedioate
**: cyclohexanesulfamate

TABLE 2



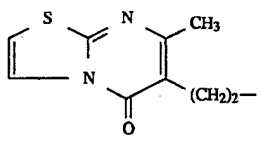
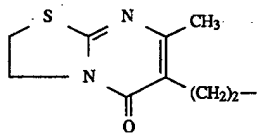
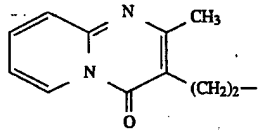
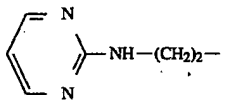
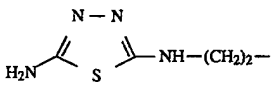
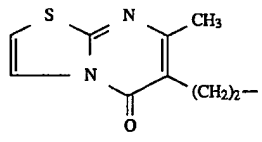
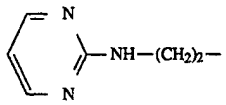
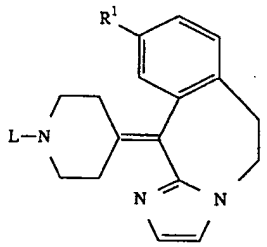
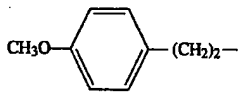
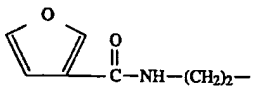
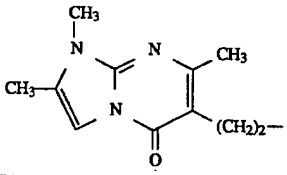
Co. No.	Ex. No.	L—	R^1	Physical data
2.01	13	CH_3—	F	mp. 195.7° C./2(E)*
2.02	19	H_5C_2OOC—	F	mp. 175.2° C.
2.03	21	H—	F	mp. 180.1° C.
2.04	31	CH_3—C(CH_3)=CH—CH_2—	F	mp. 203.4° C./2(Z)*
2.05	25		F	mp. 168.9° C./½H_2O.½(E)*
2.06	25		F	mp. 162.2° C./½H_2O.½(E)*
2.07	25		F	mp. 201.9° C./3(E)*
2.08	30	NC—CH_2—	F	mp. 198.3° C.
2.09	39	H_2N—$(CH_2)_2$—	F	—
2.10	42		F	mp. 165.1° C./3(Z)*
2.11	43		F	mp. 238.6° C.
2.12	13	H—	CH_3—	mp. 203.1° C.
2.13	24	H_5C_2OOC—	CH_3—	mp. 156.5° C.
2.14	33	CH_3—	CH_3—	mp. 214.3° C.
2.15	26		CH_3—	mp. 202.2° C.
2.16	30	NC—CH_2—	CH_3—	—
2.17	39	H_2N—$(CH_2)_2$—	CH_3—	mp. 219.3° C./3(E)*
2.18	42		CH_3—	mp. 131.1° C.

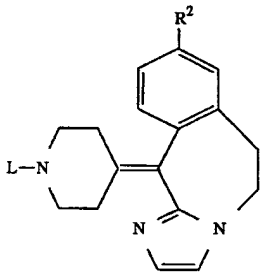
TABLE 2-continued



Co. No.	Ex. No.	L—	R^1	Physical data
2.19	26		CH_3—	mp. 192.6° C./½$(COOH)_2$
2.20	44		CH_3—	mp. 214.2° C./2(Z)*
2.21	13	CH_3—	Br	mp. 213.4° C.
2.22	25		F	mp. 187.2° C./H_2O

*: 2-butenedioate

TABLE 3



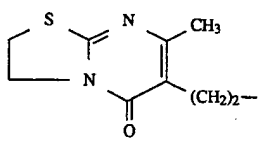
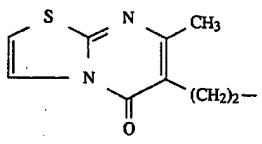
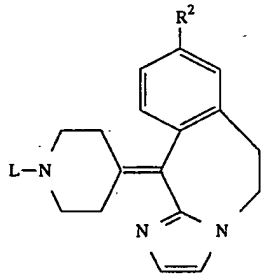
Co. No.	Ex. No.	L—	R^2	Physical data
3.01	14	CH_3—	CH_3O—	mp. 190.3° C./2(Z)*
3.02	19	H_5C_2OOC—	CH_3O—	mp. 104.4° C.
3.03	21	H—	CH_3O—	mp. 184.4° C.
3.04	13	H—	CH_3—	mp. 221.9° C./2(E)*
3.05	33	CH_3—	CH_3—	mp. 211.0° C./2(E)*
3.06	25		CH_3—	mp. 199.8° C.
3.07	25		CH_3—	mp. 214.2° C.

TABLE 3-continued



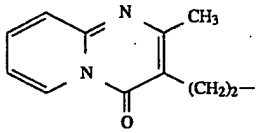
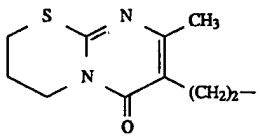
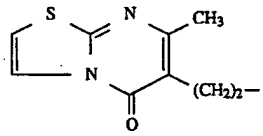
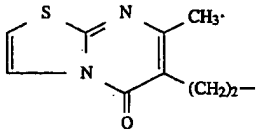
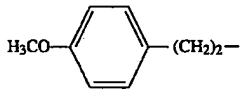
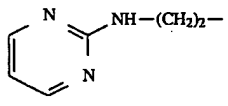
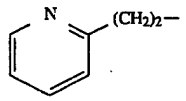
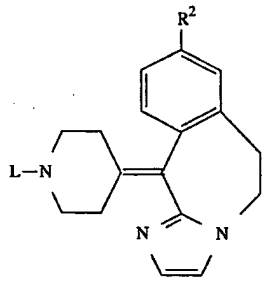
Co. No.	Ex. No.	L—	R^2	Physical data
3.08	25		CH_3—	mp. 162.3° C./H_2O.3(E)*
3.09	25		CH_3—	mp. 235.1° C./2H_2O.3HCl
3.10	13	CH_3—	Cl	mp. 186.6° C.
3.11	19	H_5C_2OOC—	Cl	mp. 140.3° C.
3.12	23	H—	Cl	mp. 197.1° C.
3.13	26		Cl	mp. 217.6° C.
3.14	30	NC—CH_2—	Cl	—
3.15	15	CH_3—	F	mp. 152.4° C.
3.16	19	H_5C_2OOC—	F	mp. 149.4° C.
3.17	21	H—	F	—
3.18	26		F	mp. 192.2° C./H_2O.3½(E)*
3.19	29		OCH_3	3/2(E)*.ethanolate/ mp. 150.3° C.
3.20	32		Cl	ethanedioate(1:2)/mp. 206.7° C.
3.21	37		Cl	mp. 171.3° C.
3.22	39	H_2N—$(CH_2)_2$—	Cl	—
3.23	28	H_5C_2—O—CO—$(CH_2)_2$—	F	mp. 114.6° C.
3.24	27	NC—CH_2—	F	mp. 204.7° C.

TABLE 3-continued



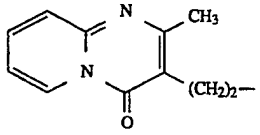
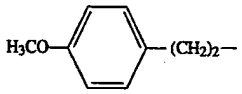
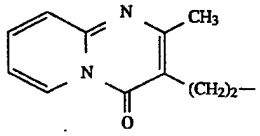
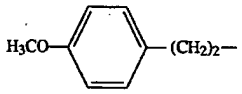
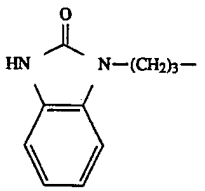
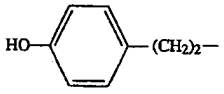
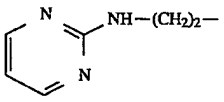
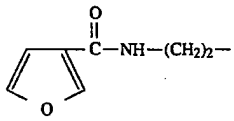
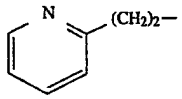
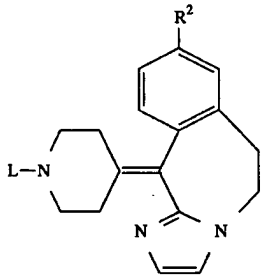
Co. No.	Ex. No.	L—	R^2	Physical data
3.25	27		F	mp. 211.6° C.
3.26	27		F	mp. 149. 1° C.
3.27	25		Cl	ethanedioate(2:5), $^1/_2$ ethanolate/mp. 170.7° C.
3.28	25		CH_3	cyclohexylsulfamate(1:2), H_2O/mp. 149.8° C.
3.29	25		CH_3	(E)-2-butenedioate(1:2), $^1/_2H_2O$/mp. 200.3° C.
3.30	58		CH_3	(E)-2-butenedioate(2:3). $^1/_2$ethanolate.$^1/_2H_2O$/ mp. 176.0° C.
3.31	57		F	$2H_2O$/mp. 136.1° C.
3.32	42		F	mp. 191.2° C.
3.33	44		F	mp. 173.5° C.
3.34	37		F	mp. 177.2° C.

TABLE 3-continued



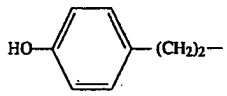
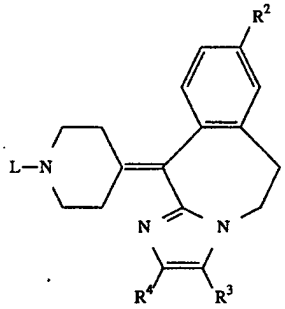
Co. No.	Ex. No.	L—	R^2	Physical data
3.35	58		F	—
3.36	39	$H_2N-(CH_2)_2-$	F	mp. 141.5° C.

TABLE 4



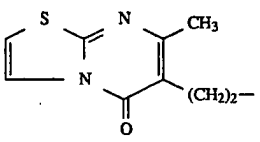
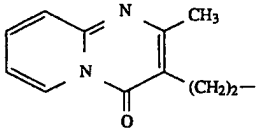
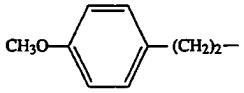
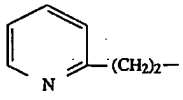
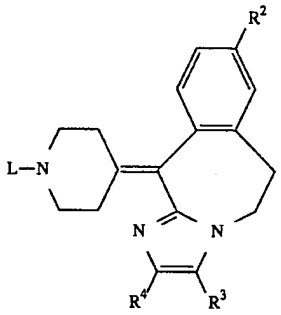
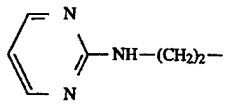
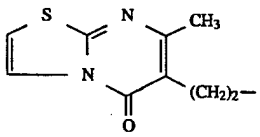
Co. No.	Ex. No.	L—	R^2	R^3	R^4	Physical data
4.01	17	CH_3-	H	H	C_6H_5	mp. 171.5° C.
4.02	13	H	H	$-CH_3$	H	mp. 167.0° C.
4.03	33	CH_3-	H	$-CH_3$	H	mp. 172.2° C.
4.04	25		H	$-CH_3$	H	mp. 212.4° C.
4.05	25		H	$-CH_3$	H	mp. 186.3° C./ 3(E)*.H_2O
4.06	25		H	$-CH_3$	H	mp. 150.6° C./ $^5/_2(COOH)_2$, H_2O
4.07	37		H	$-CH_3$	H	mp. 180.2° C./ $^7/_2(COOH)_2$
4.08	30	$NC-CH_2-$	H	$-CH_3$	H	mp. 226.5° C.
4.09	39	$H_2N-(CH_2)_2-$	H	$-CH_3$	H	—

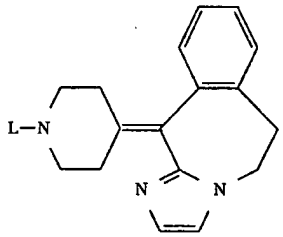
TABLE 4-continued

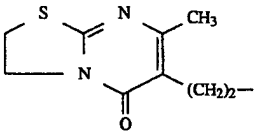
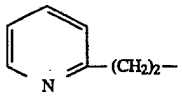
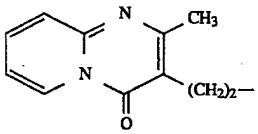
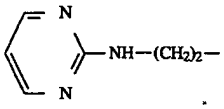
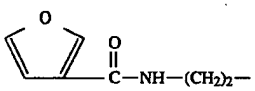
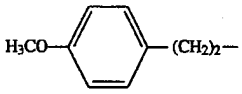


Co. No.	Ex. No.	L—	R^2	R^3	R^4	Physical data
4.10	42		H	$-CH_3$	H	mp. 171.3° C.
4.11	20	C_2H_5OOC-	H	$-CH_2OH$	H	mp. 191.9° C.
4.12	21	H	H	$-CH_2OH$	H	mp.>200° C. dec./$^5/_2$(E)*
4.13	33	CH_3-	H	$-CH_2OH$	H	mp. 228.3° C.
4.14	26		H	$-CH_2OH$	H	—
4.15	51	C_2H_5OOC-	H	$-CHO$	H	mp. 138.2° C.
4.16	51	CH_3-	H	$-CHO$	H	mp. 171.6° C.
4.17	52	C_2H_5OOC-	H	$-COOH$	H	mp. 182.2° C.
4.18	20	C_2H_5OOC-	H	$-CH_2OH$	$-CH_2OH$	—
4.19	21	H—	H	$-CH_2OH$	$-CH_2OH$	—
4.20	33	CH_3-	H	$-CH_2OH$	$-CH_2OH$	mp. 206.3° C.
4.21	36	CH_3-	H	$-CH_3$	$-CH_2OH$	mp. 166.8° C.
4.22	53	CH_3-	H	$-CH_3$	$-Br$	mp. 116.0° C.
4.23	52	CH_3-	H	$-COOH$	H	mp. 241.3° C.
4.24	51	CH_3-	F	$-CHO$	H	mp. 176.5° C.
4.25	36	CH_3-	F	$-CH_2OH$	H	mp. 181.5° C.
4.26	36	CH_3-	F	$-CH_2OH$	$-CH_2OH$	mp. 220.0° C.
4.27	54a	CH_3-	H	$-CH=CH-COOC_2H_5$	H	—
4.28	54b	CH_3-	H	$-CH=CH-COOH$	H	(E)/$^1/_2H_2O$
4.29	52	CH_3-	F	$-COOH$	H	mp. 207.3° C. $^1/_2H_2O$ mp. 261.6° C.
4.30	59a	CH_3-	H	$-CH_2-COOCH_3$	H	—
4.31	59b	CH_3-	H	$-CH_2-COOH$	H	—

* = 2-butenedioate

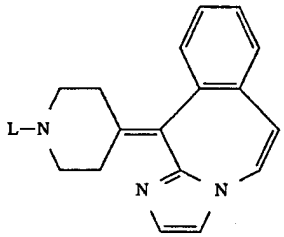
TABLE 5



Co. No.	Ex. No.	L—	Physical data
5.01	16	H—	mp. 220.2° C./ 2(E)*
5.02	34	CH_3—	mp. 117.8° C./ ½H_2O
5.03	25		mp. 221.6° C./ 2$(COOH)_2$/ $^1/_2H_2O$
5.04	37		mp. 170.3° C.
5.05	25		mp. 193.3° C.
5.06	27	NC—CH_2—	mp. 194.7° C./ ½(E)*
5.07	40	H_2N—CH_2—CH_2—	—
5.08	42		mp. 175.1° C./ 7/2(E)*
5.09	44		mp. 203.5° C.
5.10	25		cyclohexylsulfamate(1:2) $^1/_2H_2O$/ mp. 125.4° C.
5.11	24	CH_3—CO—	mp. 153.8° C.

* = 2-butenedioate

TABLE 6



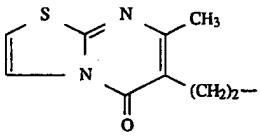
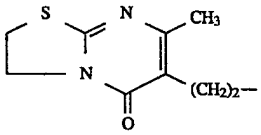
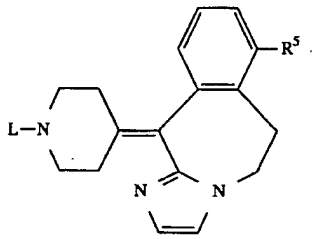
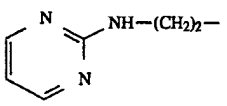
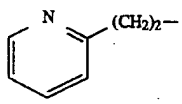
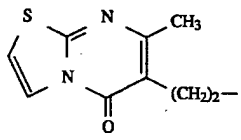
Co. No.	Ex. No.	L—	Physical data
6.01	18	CH_3—	mp. 135.8° C.
6.02	19	C_2H_5OOC—	—
6.03	22	H—	mp. 246.9° C./ 2HBr ½H_2O
6.04	27		mp. 206.4° C./ 2$(COOH)_2$ $^1/_2H_2O$
6.05	26		mp. 158.9° C./ $^5/_2(COOH)_2$ $.^1/_2H_2O$

TABLE 7



Co. No.	Ex. No.	R^5	L—	Physical data
7.01	15	—Cl	CH_3—	mp. 181.9° C.
7.02	33	$-CH_3$	CH_3—	mp. 184.2° C.
7.03	42	$-CH_3$		ethanedioate (2:7) $^1/_2H_2O$/ mp. 171.2° C.
7.04	37	$-CH_3$		(E)-2-butenedioate(2:3) $^1/_2H_2O$/162.2° C.
7.05	39	$-CH_3$	$H_2N-(CH_2)_2$—	(Z)-2-butenedioate(1:3)/ mp. 192.0° C.
7.06	13	$-CH_3$	H	—
7.07	13	$-CH_3$	H	2 HCl
7.08	13	—F	CH_3—	mp. 164.6° C.
7.09	27	$-CH_3$	NC—CH_2—	mp. 194.1° C.
7.10	25	$-CH_3$		mp. 224.3° C.

C. Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic or topical administration to warm-blooded animals in accordance with the present invention.

"Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a compound of formula (VII) wherein Q represents (C_{1-6}alkyl or phenyl)oxycarbonyl, C_{1-4}alkylcarbonyl or C_{1-6}alkyl substituted with cyano or amino, a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof.

Example 60: Oral drops

500 g of the A.I. is dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60°–80° C. After cooling to 30°–40° C. there are added 35 l of polyethylene glycol and the mixture is stirred well. Then there is added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there are added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50, l providing an oral drop solution comprising 10 mg/ml of the A.I. The resulting solution is filled into suitable containers.

Example 61: Oral solutions

9 g of methyl 4-hydroxybenzoate and 1 g of propyl 4-hydroxybenzoate are dissolved in 4 l of boiling purified water. In 3 l of this solution are dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution is combined with the remaining part of the former solution and 12 l of 1,2,3-propanetriol and 3 l of sorbitol 70% solution are added thereto. 40 g of sodium saccharin are dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence are added. The latter solution is combined with the former, water is added q.s. to a volume of 20 l providing an oral solution comprising 5 mg of the A.I. per teaspoonful (5 ml). The resulting solution is filled in suitable containers.

Example 62: Capsules

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate are vigorously stirred together. The resulting mixture is subsequently filled into 1000 suitable hardened gelatin capsules, each comprising 20 mg of the A.I.

Example 63: Film-coated tablets

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch is mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture is sieved, dried and sieved again. Then there are added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex®). The whole is mixed well and compressed into tablets, giving 10.000 tablets, each comprising 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60

HG®) in 75 ml of denaturated ethanol there is added a solution of 5 g of ethyl cellulose (Ethocel 22 cps®) in 150 ml of dichloromethane. Then there are added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol is molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole is homogenated. The tablet cores are coated with the thus obtained mixture in a coating apparatus.

Example 64: Injectable Solutions

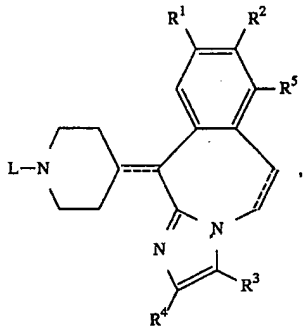
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate are dissolved in about 0.5 l of boiling water for injection. After cooling to about 50° C. there are added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I. The solution is cooled to room temperature and supplemented with water for injection q.s. ad 1 l volume, giving a solution of 4 mg A.I. per ml. The solution is sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 65: Suppositories

3 g A.I. is dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555®) q.s. ad 300 g are molten together. The latter mixture is mixed well with the former solution. The thus obtained mixture is poured into moulds at a temperature of 37°–38° C. to form 100 suppositories each containing 30 mg of the A.I.

We claim:

1. A compound of the formula:



(I)

a pharmaceutically acceptable addition salt or a stereochemically isomeric form thereof, wherein:

each of the dotted lines independently represents an optional bond;

R^1 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl, or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo;

L represents C_{1-6}alkyl; C_{1-6}alkyl substituted with one substituent selected from the group consisting of hydroxy, halo, C_{1-4}alkyloxy, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyloxy, hydroxycarbonylC_{1-4}alkyloxy, C_{1-4}alkyloxycarbonylamino, C_{1-4}alkylaminocarbonyl, C_{1-4}alkylaminocarbonylamino, C_{1-4}alkylaminothiocarbonylamino, aryl, aryloxy and arylcarbonyl; C_{1-6}alkyl substituted with both hydroxy and aryloxy; C_{3-6}alkenyl; C_{3-6}alkenyl substituted with aryl;

wherein each aryl is phenyl or phenyl substituted with halo, cyano, hydroxy, C_{1-4}alkyl, C_{1-4}alkyloxy, aminocarbonyl or phenyl substituted with C_{1-4}alkyloxycarbonyl or hydroxycarbonyl; or

L represents a radical of the formula:

—Alk—Y—Het^1 (a-1),

—Alk—NH—CO—Het^2 (a-2), or

—Alk—Y—Het^3 (a-3); wherein

Alk represents C_{1-4}alkanediyl;

Y represents O, S or NH;

Het^1, Het^2 and Het^3 each represent:

furanyl, thienyl, oxazolyl, thiazolyl or imidazolyl each optionally substituted with one or two C_{1-4}alkyl substituents;

pyrrolyl or pyrazolyl optionally substituted with formyl, hydroxyC_{1-4}alkyl, hydroxycarbonyl, C_{1-4}alkyloxycarbonyl or with one or two C_{1-4}alkyl substituents;

thiadiazolyl or oxadiazolyl optionally substituted with amino or C_{1-4}alkyl;

pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl each optionally substituted with C_{1-4}alkyl, C_{1-4}alkyloxy, amino, hydroxy or halo; or

imidazo[4,5-c]pyridin-2-yl;

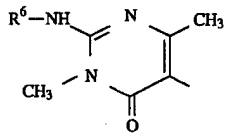
and Het^3 may also represent a member selected from the group consisting of:

(a) 4,5-dihydro-5-oxo-1H-tetrazolyl substituted with C_{1-4}alkyl;

(b) 2-oxo-3-oxazolidinyl;

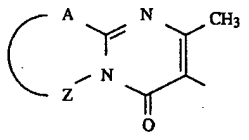
(c) 2,3-dihydro-2-oxo-1H-benzimidazol1-yl; and

(d) a radical of the formula:



(b-1)

or



(b-2)

wherein:

R^6 represents hydrogen or C_{1-4}alkyl; and

A-Z represents —S—CH=CH—, —S—CH_2—CH_2—, —S—CH_2—CH_2—CH_2—, —CH=CH—CH=CH—, —CH_2—CH_2—CH_2—CH_2—, —N(CH_3)—C(CH_3)=CH— or —CH=C (CH_3)—O—.

2. A compound according to claim **1** wherein L is C_{1-4}alkyl or C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl.

3. A compound according to claim **1** wherein:

R^3 represents hydrogen, C_{1-4}alkyl, formyl, hydroxyC_{1-4}alkyl or hydroxycarbonyl;

R^4 represents hydrogen, halo or hydroxyC_{1-4}alkyl; and

L represents C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylaminoC_{1-4}alkyl, arylC_{1-4}alkyl, propenyl, or

L is a radical of the formula:

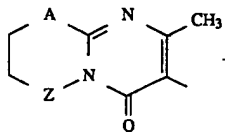
—Alk—Y—Het^1 (a-1),

—Alk—NH—CO—Het^2 (a-2), or

—Alk—Y—Het^3 (a-3); wherein

Het^1, Het^2 and Het^3 each represent furanyl oxazolyl, or thiazolyl each optionally substituted with C_{1-4}alkyl; thiadiazolyl optionally substituted with amino; pyridinyl; pyrimidinyl optionally substituted with hydroxy; or imidazo[4,5-c]pyridin-2-yl;

or Het^3 may also represent a radical of the formula (b-2):



(b-2)

4. A compound according to claim 3 wherein

R^1 represents hydrogen or halo;

R^2 represents hydrogen, halo or C_{1-4}alkyloxy; and

L represents hydrogen, C_{1-4}alkyl, haloC_{1-4}alkyl, hydroxycarbonylC_{1-4}alkyl, C_{1-4}alkyloxycarbonylC_{1-4}alkyl, or a radical of formula (a-1), wherein Y represents NH.

5. A compound according to claim 1 wherein said compound is selected from the group consisting of

5,6-dihydro-11-(1-methyl-4-piperidinylidene)-11 H-imidazo[2,1-b][3]benzazepine;

9-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine;

11-(1-methyl-4-piperidinylidene)-11 H-imidazo[2,1-b][3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3] benzazepine-3-methanol;

8-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1-b][3]benzazepine;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-H-imidazo[2,1-b][3]benzazepine-3-carboxaldehyde;

6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5 H-imidazo[2,1-b][3] benzazepine-3carboxylic acid;

7-fluoro-6,11-dihydro-11-(1-methyl-4-piperidinylidene)-5H-imidazo[2,1 -b][3]benzazepine; and

4-(8-fluoro-5,6-dihydro-11 H-imidazo[2,1-b][3]benzazepin- 11-ylidene)-1-piperidinepropanoic acid dihydrate.

6. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 1 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 2 and a pharmaceutically acceptable carrier.

8. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 3 and a pharmaceutically acceptable carrier.

9. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 4 and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising as an active ingredient a therapeutically effective amount of a compound as defined in claim 5 and a pharmaceutically acceptable carrier.

11. A method of treating allergic conditions in warm blooded animals which comprises administering to warm blooded animals suffering from allergic conditions an effective anti-allergic amount of a compound as defined in claim 1.

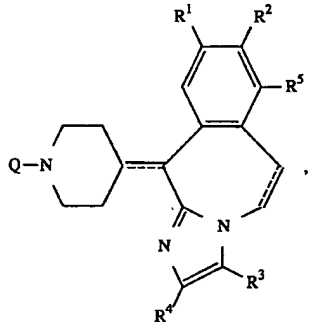
12. A method of treating allergic conditions in warm blooded animals which comprises administering to warm blooded animals suffering from allergic conditions an effective anti-allergic amount of a compound as defined in claim 2.

13. A method of treating allergic conditions in warm blooded animals which comprises administering to warm blooded animals suffering from allergic conditions an effective anti-allergic amount of a compound as defined in claim 3.

14. A method of treating allergic conditions in warm blooded animals which comprises administering to warm blooded animals suffering from allergic conditions an effective anti-allergic amount of a compound as defined in claim 4.

15. A method of treating allergic conditions in warm blooded animals which comprises administering to warm blooded animals suffering from allergic conditions an effective anti-allergic amount of a compound as defined in claim 5.

16. A compound of the formula:



(VII)

an acid addition salt thereof or a stereochemically isomeric form thereof, wherein each of the dotted lines independently represents an optional bond, and wherein:

R^1 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^2 represents hydrogen, halo, C_{1-4}alkyl or C_{1-4}alkyloxy;

R^3 represents hydrogen, C_{1-4}alkyl, ethenyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, C_{1-4}alkyl substituted with hydroxycarbonyl or C_{1-4}alkyloxycarbonyl, hydroxyC_{1-4}alkyl, formyl or hydroxycarbonyl;

R^4 represents hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, phenyl or halo;

R^5 represents hydrogen, C_{1-4}alkyl or halo; and

Q represents phenyloxycarbonyl, or C_{1-6}alkyl substituted with a member selected from the group consisting of halo, cyano, amino, isothiocyanato, (4-amino-3 -pyridinyl)aminothiocarbonylamino, $(CH_3O)_2CH—CH_2—NH—C(=NCH_3)—NH—$, and methylsulfonyloxy.

* * * * *

Exhibit 5

Copy of the USPTO Maintenance Fee Statement

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Customer No 000000

ISTMT

DATE PRINTED
08/26/2010

AUDLEY A. CIAMPORCERO
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK NJ 08933-7003

MAINTENANCE FEE STATEMENT

According to the records of the U.S.Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed below. The "PYMT DATE" column indicates the payment date (i.e., the date the payment was filed).

The payment shown below is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.

Direct any questions about this statement to: Mail Stop M Correspondence, Director of the USPTO, P.O.Box 1450, Alexandria, VA 22313-1450.

PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
5,468,743	$3,800.00	$0.00	04/27/07	08/142,474	11/21/95	11/29/93	12	NO	JAB812PCTUS

Return To USPTO Home Page

Finance Online Shopping Page

United States Patent and Trademark Office

Patent Bibliographic Data				08/26/2010 01:36 PM	
Patent Number:	5468743		Application Number:	08142474	
Issue Date:	11/21/1995		Filing Date:	11/29/1993	
Title:	IMIDAZO[2,1-B]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE				
Status:	4th, 8th and 12th year fees paid			Entity:	Large
Window Opens:	N/A	Surcharge Date:	N/A	Expiration:	N/A
Fee Amt Due:	Window not open	Surchg Amt Due:	Window not open	Total Amt Due:	Window not open
Fee Code:					
Surcharge Fee Code:					
Most recent events (up to 7):	04/27/2007	Payment of Maintenance Fee, 12th Year, Large Entity.			
	04/22/2003	Payment of Maintenance Fee, 8th Year, Large Entity.			
	04/20/1999	Payment of Maintenance Fee, 4th Year, Large Entity.			
		--- End of Maintenance History ---			
Address for fee purposes:	AUDLEY A. CIAMPORCERO ONE JOHNSON & JOHNSON PLAZA NEW BRUNSWICK, NJ 089337003				

Run Another Query

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Exhibit 6

Certificate of Correction and Supporting Documentation

PTO/SB/44 (09-07)
Approved for use through 08/31/2010. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,468,743

APPLICATION NO.: 08/142474

ISSUE DATE : November 21, 1995

INVENTOR(S) : Frans E. Janssens, Gaston S. M. Diels, Joseph E. Leenaerts

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

The title on the cover of the issued patent contains a typographical error. It incorrectly left out "[3]". The correct title should be:

IMIDAZO[2,1-B][3]BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE

MAILING ADDRESS OF SENDER (Please do not use customer number below):

Philip S. Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Acknowledgement Receipt

The USPTO has received your submission at **11:42:14** Eastern Time on **23-SEP-2010** by Deposit Account: 100750.

$ **100** fee paid by e-Filer via *RAM* with Confirmation Number: 9851.

eFiled Application Information

EFS ID	8480374
Application Number	08142474
Confirmation Number	8874
Title	IMIDAZO[2,1-B] BENZAZEPINE DERIVATIVES, COMPOSITIONS AND METHOD OF USE
First Named Inventor	FRANS E. JANSSENS
Customer Number or Correspondence Address	AUDLEY A. CIAMPORCERO ONE JOHNSON & JOHNSON PLAZA NEW BRUNSWICK NJ 089337003 US
Filed By	Ruby T. Hope/Karen Hall Morgan
Attorney Docket Number	JAB812PCTUS
Filing Date	29-NOV-1993
Receipt Date	23-SEP-2010
Application Type	U.S. National Stage under 35 USC 371

Application Details

Submitted Files	Page Count	Document Description	File Size	Warnings
certificateofcorrection.pdf	2	Request for Certificate of Correction	38952 bytes	PASS
fee-info.pdf	2	Fee Worksheet (PTO-875)	30361 bytes	PASS

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance

of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

If you need help:

- *Call the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent e-Filing.*
- *Send general questions about USPTO programs to the USPTO Contact Center (UCC) .*
- *If you experience technical difficulties or problems with this application, please report them via e-mail to Electronic Business Support or call 1 800-786-9199.*

Exhibit 7

Description of Significant Activities of Applicant During Regulatory Review Period

Description of Significant Activities of Applicant During Regulatory Review Period

Submission Log IND 66,884

Amendment Date:	Description:
10/21/2003	Pre-IND FDA Meeting Request
11/3/2003	Pre-IND Meeting Package
11/24/2003	ORA Meeting Minutes from FDA Pre-IND Meeting
3/18/2004	Request for toxicology guidance prior to IND filing (missing signed letter)
4/2/2004	FDA response to Vistakon questions
7/1/2004	S-000. Original IND Submission
7/2/2004	S-001. Amendment to Original IND Toxicology (signed letter missing)
7/16/2004	FDA Request for Information regarding CM&C
7/30/2004	FDA Comments on Original IND Submission: clinical, IB, formulation
7/30/2004	Response to FDA comments sent 7/30/2004 (clinical)
8/4/2004	S-002. Address FDA comments, amended IB, Amendment 04-003-09, statistical plan 04-003-09
8/16/2004	S-003. Request for CM&C Teleconference
9/21/2004	Clarification of FDA comments of 7/30/2004 & additional FDA comments
9/28/2004	S-004. Summary results of 04-003-09, amendment to 04-003-10, investigator information
10/18/2004	S-005. Amendment Clinical Information
11/1/2004	S-006. Amendment CM&C
11/3/2004	S-007. CM&C amendment
11/12/2004	FDA Fax. FDA Reviewer comments: General, 04-003-15, 04-003-16 and chemistry.
11/17/2004	E-mail of FDA comments on 8/5/04 and 9/5/04 submissions (clinical)
11/22/2004	EOP2 FDA Meeting Request
11/23/2004	S-008. Response to FDA comments received 11/17/2004
12/9/2004	E-mail to FDA containing preliminary questions for FDA reviewer & electronic copy of meeting request
1/3/2005	S-009. End of Phase II Meeting Briefing Package
1/6/2005	Response to FDA comments on Amendment 004 dated 9/28/2004
1/27/2005	EOP2 Vistakon Meeting Questions and FDA correspondence
3/15/2005	S-010. Request for teleconference with chemistry reviewer in response to FDA comments on EOP2 meeting package dates 1/3/2005
3/18/2005	S-011. Protocol 05-003-004, Investigator data and CMC information
3/22/2005	FDA confirmation of meeting scheduled on 5/6/2005

3/28/2005	S-012. Statistical Analysis plan to support Protocol 05-003-04
4/6/2005	FDA comments on 011 dated 3/18/2005, CM&C
4/27/2005	E-mail from FDA: response to meeting package for meeting 5/6/2005
4/29/2005	S-013. Response to FDA request for information (clinical and CMC)
5/2/2005	Questions/ Clarification Request to FDA about the API
5/4/2005	FDA clarifications on fax of 3/18/2005
5/5/2005	E-mail of slides to FDA in preparation for meeting on May 6
5/9/2005	Response to FDA e-mail 5/4/2005
5/17/2005	Clinical Reviewer comments on 3/28/2005 submission
6/2/2005	Official FDA meeting minutes from the 5/6/2005 CMC meeting.
6/20/2005	S-014. Responses to two sets of inquiries for information.
7/8/2005	S-015. Request for special protocol assessment - Phase III Clinical protocol 05-003-11.
7/8/2005	S-016. Request for special protocol assessment - Phase III Clinical protocol 05-003-13.
7/11/2005	S-017. Request for special protocol assignment - Phase III Clinical protocols 05-003-09 and 05-003-10.
8/17/2005	FDA response to a July 7, 2005 Special Clinical Protocol Assessment S-0015 for protocol #05-003-11.
8/18/2005	FDA response to a July 8, 2005 Special Clinical Protocol Assessment S-0016 for protocol #05-003-13.
8/26/2005	S-018. 28-Day Interim Report: 05-2456-GI, "A 6 Month Repeat Dose Ocular Toxicity Study in Rabbits" and topline summary of toxicokinetic data.
9/7/2005	S-019. CMC updates to the drug substance and drug product sections of the IND.
9/14/2005	S-020. Amended protocols 05-003-09 (PK study) and 05-003-10 (safety study).
9/21/2005	S-021. Information Amendment: Amended protocol 05-003-11, statistical analysis plan, and facilities data/investigator information.
9/29/2005	S-022. Information Amendment: Amended protocols 05-003-09, 05-003-11, 05-003-10.
11/8/2005	S-023. Information Amendment: New protocol: 05-003-20, facilities/investigator information: Protocols 05-003-20 and 05-003-10.
11/23/2005	S-024. Annual Report for period 8/1/04 to 7/31/05
11/28/2005	Internal e-mail regarding e-mail correspondence with FDA in order to obtain the statistical reviewer's information for this IND.
1/31/2006	S-025. Request for a pre-NDA meeting.
3/10/2006	S-026. Notice of intent to file the NDA for this product electronically in Common Technical Document (CTD) format; e-submission contact is Jacqueline U. Linse.
3/28/2006	S-027. Additional information on Compound 465199 as a starting material for the manufacture of drug substance, as requested by FDA
3/28/2006	S-028. Pre-NDA meeting package
4/26/2006	List of meeting participants for Pre-NDA meeting on April 26, 2006
4/26/2006	Meeting minutes for Pre-NDA meeting of April 26, 2006
5/4/2006	Pre-NDA minutes from meeting of 4/26/06, and emails
5/8/2006	Fax from FDA in response to our Sub. Ser. No. 027, FDA says use of compound 465199 as a starting material is acceptable

6/5/2006	S-029. Submission to FDA of clarification of questions raised at pre-NDA meeting of April 26, 2006
6/16/2006	S-030. Proposed Pediatric Study Request
7/11/2006	S-031. Carcinogenicity Waiver Request
8/4/2006	S-032. Information Amendment: New protocol 06-003-09
8/22/2006	S-033. Submission to FDA of a proposed proprietary name for provisional acceptance: Vilasta; request Division, DDMAC and DMETS reviews
8/23/2006	S-034. Submission of the statistical analysis plan for protocol 06-003-09
8/28/2006	Email from R. Rodriguez, FDA to M. Chapin, PPC; comments of the clinical reviewer on items discussed at 4/26/06 meeting
8/28/2006	Email from R. Rodriguez, FDA to M. Chapin, PPC; reviewer's comments on proposed pediatric study request
9/13/2006	Email from Matthew Chapin to Stephenie Barba on carcinogenicity waiver
9/22/2006	Email from R. Rodriguez, FDA, containing the comments of the clinical reviewer concurred by Dr. Chambers
9/22/2006	Email from R. Rodriguez, FDA, regarding FDA review of the application; L. Kim-Jung, FDA, requests labels/labeling
10/25/2006	S-035. Meeting Request regarding changes to packaging
11/14/2006	S-036. Meeting Request
11/15/2006	Email from FDA stating they have received the meeting request.
11/22/2006	Letter from FDA regarding meeting request of 11/14/06; FDA has concluded meeting is not necessary
11/22/2006	Email from Matthew Chapin to Stephenie Barba on response from FDA regarding meeting request.
11/28/2006	S-037. Response to FDA's comments on Protocol 06-003-09, submitted 8/4/06
12/6/2006	Email from Raphael Rodriguez, FDA, to Matthew Chapin: comments of the CMC leader for ophthalmology, Dr. Linda Ng.
12/11/2006	Email from Linda Mullins Athey, FDA, to Donna Welch, Vistakon Pharmaceuticals, preliminary responses from FDA on questions and additional comments
12/11/2006	Email from Matthew Chapin to Stephanie Barba, attaching FDA's email of preliminary responses from agency
12/12/2006	S-038. Annual Report for period 8/1/05 to 7/31/06
4/23/2007	Email from Matthew Chapin to Stephanie Barba and Maria Kang, regarding FDA's response to the VILASTA tradename review. DMETS has no objections to the use of this name, though this is a tentative decision.
11/16/2007	Annual Report 8/1/06 to 7/31/07
11/19/2007	Information Amendment: Pharm/Tox. Submission of final study report 05-6067-G1 for "A 14 Day Repeat Dose Ocular Toxicity Study in Rabbits for R89674 and Impurities."
11/30/2007	Information Amendment: Clinical. Submission of final study report 04-003-09, "A Single Center, Randomized, Double Masked, Contralateral Comparison of the Safety and Comfort of Four Concentrations of R89674 Ophthalmic Solution as Compared to Tears Naturale(R) II (Placebo) in Subjects with Normal Ocular Health".

11/30/2007	Information Amendment: Clinical. Submission of final study report 04-003-10, "A Prospective, Single-Center, Double-Masked, Randomized, Placebo and Active Controlled, Evaluation of the Duration of Action of R89674 Ophthalmic Solution in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis at 15 Minutes and 16 Hours After Instillation".
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-04, "A Single Center, Randomized, Double Masked, Contralateral Comparison of the Safety and Comfort of Three Formulations of R89674 0.25% Ophthalmic Solution as Compared to Tears Naturale(R) II (Placebo) in Subjects with Normal Ocular Health".
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-09, "A Prospective, Single-Center, Open Label Study of the Plasma Pharmacokinetics and Safety following Topical Administration of R89674 0.25% Ophthalmic Solution as a Single and Repeated Dose in Healthy, Adult Subjects."
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-10, "A Multicenter, Randomized, Double-Masked, Vehicle-Controlled, Parallel-Group Study Evaluating the Safety of R89674 0.25% Ophthalmic Solution Used Once Daily in Healthy, Normal Volunteers."
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-11, "A Multicenter, Double-Masked, Randomized, Placebo Controlled, Evaluation of the Onset and Duration of Action of R89674 0.25% Ophthalmic Solution in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis."
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-20, "A Single-Center, Double-Masked, Randomized, Placebo Controlled, Evaluation of R89674 0.25% Ophthalmic Solution in a Relief Model Using the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis."
11/30/2007	Information Amendment: Clinical. Submission of final study report 05-003-13, "A Single-Center, Double-Masked, Randomized, Placebo Controlled, Evaluation of the Onset and Duration of Action of R89674 0.25% Ophthalmic Solution in the Conjunctival Allergen Challenge (CAC) Model of Acute Allergic Conjunctivitis."
8/18/2008	Information Amendment - Chemistry; Protocol Amendment - New Protocol 07-003-10
9/30/2008	Annual Report 8/1/07 to 7/31/08
11/10/2008	Chemistry & Clinical Request for Feedback - minor changes to formulation
11/17/2008	Info Amendment - Pharm/Tox - Final Study Report P1006064
11/17/2008	Info Amendment - Pharm/Tox - Final Study Reports AAL00003, 07-003-091, 870580
11/17/2008	Info Amendment - Pharm/Tox - Final Study Reports N111678, N125298
11/18/2008	Ltr from ORA stating that Amendments 052, 053, 054 were submitted to FDA on 11/17/08
12/16/2008	Info Amendment - Pharm/Tox - Final Study Reports 961392, 961393
3/31/2009	Correspondence from Ora to FDA: IND 66,884 Alcaftadine (R89674) Ophthalmic Solution, 0.25%, New Amendment: New Protocol and Investigators - 09-003-05; Serial No. 0056
9/28/2009	Annual Report 8/1/08 to 7/31/09
	HOLD FOR Info Amendment - Clinical - Final Study Report 06-003-09

	HOLD FOR Info Amendment - Clinical - Final Study Report 07-003-10
	HOLD FOR Info Amendment - Clinical - Final Study Report 09-003-05
9/29/2009	Correspondence from Ora to FDA: "RE: IND 66,884 Alcaftadine (R89674) Ophthalmic Solution, 0.25%, Information Amendment - Clinical, Serial No. 0058": Regarding submission of Final Study Report for Protocol 06-003-09; included FDA Forms 1571 & 3674
9/29/2009	Correspondence from Ora to FDA: "RE: IND 66,884 Alcaftadine (R89674) Ophthalmic Solution, 0.25%, Information Amendment - Clinical, Serial No. 0059": Regarding submission of Final Study Report for Protocol 07-003-10; included FDA Forms 1571 & 3674
9/29/2009	Correspondence from Ora to FDA: "RE: IND 66,884 Alcaftadine (R89674) Ophthalmic Solution, 0.25%, Information Amendment - Clinical, Serial No. 0060": Regarding submission of Final Study Report for Protocol 09-003-05; included FDA Forms 1571 & 3674

Submission Log NDA 22-134

Date	Description
9/29/2009	0000 Original NDA in eCTD format
10/6/2009	0001 Pediatric Waiver Assessment
10/8/2009	Email from R. Rodriguez (FDA): NDA 22134 Proprietary name guidance: Also acknowledged receipt of pediatric waiver submission
10/28/2009	0002 Proprietary Name Request
10/28/2009	Email to R. Rodriguez & B. Dorch (FDA): "NDA 022134 - Request for Review of Proprietary Name": Reported submission of Request for Review of Proprietary for Vilasta on 10/28/09; reference to acknowledgement of electronic receipt of submission
10/30/2009	Email from R. Rodriguez (FDA): "NDA 22134 Stat Information Request": Forwarded Information Requests (IR) from statistical reviewer; requested response by 11/6/09
11/3/2009	Email to R. Rodriguez (FDA): Response to "RE: NDA 22134 Stat Information Request": Regarding response to FDA's information request
11/11/2009	Email to R. Rodriguez (FDA): "RE: NDA 022134 Stat Information Request": Referred to phone conversation on 11/5/09 regarding preparation of complete response to IR's from statistical reviewer; stated projected response should be received via Electronic Submissions Gateway by COB 11/16/09
11/16/2009	0003 Response to FDA request for Information: SAPs and Randomization Datasets
11/17/2009	Email to R. Rodriguez (FDA): "RE: NDA 022134 Stat Information Request": Reported response was received via Electronic Submissions Gateway
11/19/2009	0004 Response to request for Patient Data Listings
11/19/2009	Email to R. Rodriguez (FDA): "Information Request - Medical officer - DSI": Information Request received from Medical Officer in DSI; MO requested Patient Data Listings for Study 09-003-05 and 05-003-11, which were sent on 11/19/09 via the ESG & were received
12/7/2009	Email from R. Rodriguez (FDA): "CMC Comments for NDA 22-134": FDA comments forwarded in email - reference to proposed starting material discussed in EOP2 meeting; additional information requested
12/10/2009	0005 Response to FDA request for Information: CM&C (Starting Material)
12/11/2009	Letter From FDA: "Filing Communication": Reference to NDA dated 9/29/09, received 9/29/09; notification of completion of filing review; review classification - Standard; Vilasta (alcaftadine ophthalmic solution), 0.25%
12/21/2009	Email from R. Rodriguez (FDA): "FW: NDA 22-134, CMC comments": Contains chemistry information requests; request for response by 1/5/10
1/4/2010	0006 Email Response to FDA request for Information: "RE: NDA 22-134, CMC comments": Notification of responses submitted via the ESG; reference to request for telecon to discuss Questions 3 & 5 regarding test and acceptance criterion for endotoxin in drug product, from queries received on 12/7/09
1/6/2010	Email To/From Michael Serrano (FDA): "RE: Inspection": Request for/confirmation of inspection site location (initially sent on 12/28/09)

1/8/2010	Email From R. Rodriguez (FDA): "RE: NDA 022134": Reference to Advisory Committee meeting regarding NDA; remarked no decisions of product going to AC meeting
1/20/2010	Email to Jeannie David (FDA): "NDA 022134 CMC Telecon": Reference to previous phone conversation & response to FDA request for Telecon to discuss 12/7/09 CMC Information Request Question #5 & 12/21/09 CMC Information Request Question #3; confirmed telecon for 1/22/10, 9-9:30 am
1/20/2010	Email from L. J. Bremer: "FDA Call": Reference to phone conversation w/Jeannie David, CMC Project Manager (FDA); requested rescheduling of telecon (re. CMC Information Request Questions) to 8:30 am
1/28/2010	0007 4 Month Safety Update
1/29/2010	0008 Response to FDA request for Information: CM&C Clarification of Jan. 2, 2010 Submission
2/2/2010	Email from L. J. Bremer to R. Rodriguez (FDA): "RE: NDA 22-134 Protocol 06-003-09": Response to initial request for information (on 2/1/10) regarding number of patients enrolled in age group 10-17 years old for clinical trial 06-003-09; also acknowledged receipt of Sequence 0008 on 1/29/10, response to additional CMC questions raised in telecon w/Chemistry reviewers on 1/22/10 & revision to response to Question #3 Chemistry Information request received 12/7/09
2/18/2010	Email from L. J. Bremer: "FDA Request": Forwarded request from FDA for summary of data for safety & efficacy for 27 patients aged 10-17 enrolled in clinical trial 06-003-09; VILASTA (alcaftadine) Ophthalmic Solution 0.25%
2/18/2010	Email from R. Rodriguz (FDA): "RE: RE: NDA 22-134 Protocol 06-003-09": Request from FDA for summary of data for safety & efficacy for 27 patients aged 10-17 enrolled in clinical trial 06-003-09; VILASTA (alcaftadine) Ophthalmic Solution 0.25%
2/24/2010	Email From R. Rodriguez (FDA): "FW: NDA 22-134: a request to sponsor": Forwarded Stat Information Request (IR); requested further clarification on the assignment of treatment to the eyes in studies 05-003-11 & 05-003-13
2/25/2010	0009 Response to Clinical Information request study 06-003-09
3/3/2010	Email From R. Rodriguez (FDA): "Comments for NDA 022-134": CMC information request
3/4/2010	0010 Response to Statistical Information Request
3/11/2010	Email From R. Rodriguez (FDA): "FW: NDA 22134: Stat Information Request": Forwarded stat comments regarding J&J's recent responses to information request; responses found to be insufficient
3/23/2010	0011 Response to Statistical Information Request
3/31/2010	0012 Response to CMC Request for Information - Drug Substance
4/15/2010	0013 Proprietary Name Rebuttal
4/22/2010	0014 CMC Information

4/23/2010	0015 Email To R. Rodriquez (FDA): "RE: NDA 022-134 CMC information requests": Question regarding CMC Information Request Item No. 4 (initially submitted by FDA on 4/22/10
4/28/2010	Email To D. Brantley & R. Rodriquez (FDA): "RE: Teleconference participants for NDA 022134": Confirmation of telecon for 5/12/10, 11-11:30
4/29/2010	Email from R. Rodriguez: "NDA 22134 regarding study report N 125328": Forwarded information request from biopharm reviewer regarding the in vitro metabolism study report N 125328; also, response email to FDA from L. J. Bremer indicating response to CMC information request (4/21/10) was recently received at ESG
4/29/2010	0015 Response to FDA CMC Request of April 21
5/3/2010	Email from R. Rodriguez: "FW: NDA 22134 regarding study report N 125328": Forwarded additional information request from CMC reviewer regarding NDA 22-134, Sequence No. 0015; also, response email to FDA from L. J. Bremer indicating receipt of CMC information request & submission of Sequence 0016 (received at ESG)
5/3/2010	Email from L. J. Bremer to R. Rodriguez: "RE: NDA 22134 regarding study report N 125328": Notification of resubmission of Sequence No. 0015 (initially sent on 4/29/2010); also, Sequence 0016 received at ESG on 5/3/2010
5/3/2010	0016 Replacement for submission sent under 0015 due to inactive hyperlinks
5/6/2010	Email From L. J. Bremer To D. Brantley & R. Rodriquez (FDA): "RE: Teleconference participants for NDA 022134": Advised FDA of decision to rescind Request for Reconsideration of the Proprietary Name "Vilasta" & submission of alternate name; official letter to be sent via ESG on 5/7/10; no need for 5/12/10 telecon
5/7/2010	0017 Response to FDA CMC Request of May 3, 2010
5/7/2010	0018 Recindment of Request for Reconsideration of Proprietary name (Sequence 0013)
5/12/2010	0019 Request for Review of Proprietary name "Vylasta"
5/26/2010	0020 Response to Request for CMC Information received May 11, 2010
5/28/2010	0021 Response to FDA Biopharm Reviewer Questions From April 29, 2010
6/10/201	0022 Response to Labeling Comments of May 25, 2010
6/25/2010	0023 Submission of font sizes in SOI on carton and bottle label
7/7/2010	0024 Rescind Request for Review of Proprietary Name Vylasta & Proposal of two alternatives
7/8/2010	0025 Response to Request for Bottle and Carton Labels without a tradename
7/20/2010	0026 Officially Submit Lastacaft as the preferred product name (prior submission listed two potentials)
7/22/2010	0027 Submission of Revised Labeling
7/28/2010	Approval Letter